THE INBORN FACTORS IN DISEASE

AN ESSAY

BY

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PREFACE

THIS essay had its origin in the Huxley Lecture on 'Diathesis' delivered by its author at the Charing Cross Hospital in 1927.

In it the bearings of more recent scientific advances upon the problems of disease are discussed more fully than was possible in a single lecture.

Its pages reflect the outlook of a student of medicine of fifty years' standing who began his medical studies shortly before the discovery of the tubercle bacillus, and has witnessed the advances of, and the profound changes in, medicine and surgery during the most fruitful half-century in their history.

The author takes this opportunity to express his sincere gratitude to all those who have helped him in various ways, and especially to Sir Frederick Andrewes and Professor F. R. Fraser for their valued criticism and advice.

December 1930.

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Prologue

THE DOCTRINES OF DIATHESIS

Dupes d'un mot, les médecins ont cru pendant longtemps, et la plupart croient encore avoir donné la clef de ces phénomènes aussitôt qu'ils ont dit: Ce sont des diathèses, et cette croyance empêche d'en chercher une autre explication.—L. F. ROCHE. 1831.

FAR back, in the early days of medical knowledge, it was recognized that some individuals are more, and others less liable to this or that disease; and it was known at least as early as the commencement of the Christian era, that diseases may be handed down from parents to children.

Towards the end of the eighteenth century, at a time when clinical medicine was beginning to be set upon a firmer basis than it had had for centuries previously; not only by increased study of morbid anatomy, but also by the introduction of new methods for the detection of local lesions, and especially auscultation and percussion, there was also a great awakening of interest in less tangible matters, the morbid predispositions and the so-called temperaments.

At that time, and indeed through the greater part of the nineteenth century, it was in the French Schools of Medicine that such matters were most actively discussed, and much of the discussion centred around the word 'diathesis'.[1]

[1] For an admirable history of the Doctrines of Diatheses, *see* André Leri, *Progrès Méd.*, 1912, xl. 141 et seq

No little interest attaches to the history of this phase of medical doctrine, although it appears to us to-day that much of the pursuit of the diatheses was carried out in a fog, and led the pursuers along tangled ways. At any rate some account of the stages of the pursuit is highly desirable, if not essential, as an introduction to any discussion of the inborn factors in disease, as these appear when examined in the light of more recent scientific advances.

Widely different meanings have been attached to the word diathesis, at different times, in different countries and medical schools, and even by individual members of the same school. These differences are largely responsible for the disfavour into which the term has fallen; they are so fundamental that they deprive the name diathesis of all practical utility; and reluctant as one must needs feel to abandon a time-honoured designation, this particular one has become so damaged by conflicting uses that its employment, in any modern sense, is calculated to lead to fresh confusion. That being so, it seems better to lay it aside.

It may be recalled that the original meaning of διάθεσις, was an arrangement of objects in space, their disposition, and hence *a* disposition. In more recent usage, the meaning attached to the word has been a disposition, or predisposition, to a particular malady or group of maladies. It is in this sense that it has been employed by the great majority of English writers and teachers.

Thus, in some manuscript notes of a course of lectures on medicine, delivered in 1841/2, by C. B. J. Williams, one of the leading teachers of his day, there occurs the following passage: 'Diathesis is merely a disposition to a disease, it gives no idea of its cause.' The word diathesis is not to be found in the indexes of the great majority of English text-books of Medicine, published during the last fifty years. In the *New English Dictionary*, in a volume (D), which was published in 1897, diathesis is defined as 'a permanent (hereditary or acquired) condition of the body, which renders it liable to certain special diseases or affections; a constitutional predisposition or tendency'. The words printed in brackets (as in the original) raise a highly controversial question, and clearly reflect the teaching of Jonathan Hutchinson.

Undoubtedly a diathesis has always been thought of by the great majority of physicians in this country, as an inborn, and usually inherited predisposition.

In the French schools, on the other hand, there early became manifest a tendency to apply the name to predisposition to the manifestations of a disease, rather than to the disease as such.

Thus, he who developed a succession of abscesses was regarded as the subject of a purulent diathesis, he who bled frequently of a haemorrhagic diathesis, a name which is still occasionally applied to the disease haemophilia. Bazin enumerated a number of such diatheses, calcareous, saccharine, fatty, fibrinous, and the like.

On the other hand there were always members of the French school who did not share the prevalent views, and amongst them Roche,[1] as the quotation at the head of this chapter shows.

Towards the middle of the nineteenth century the conceptions had become narrowed down and assumed more definite form. A diathesis came to be looked upon as a comparatively slight deviation from normality, a 'peculiarity of health' as Hutchinson[2] called it, or in the words of Germain Sée:[3] 'Cet état intermédiaire qui n'est pas encore la maladie, mais qui n'est déjà plus la santé parfaite.'

Just as in a mushroom-bed a hidden, underground mycelium throws up mushrooms here and there, and from time to time, so the diathesis is regarded as latent, but its presence is revealed by the manifestations to which it gives rise from time to time. It is easy to see how largely the phenomena of gout, which has always been regarded as the typical diathetic disease, have been instrumental in shaping this conception.

In Nysten's Dictionary, published in 1858, diathesis was defined as a general disposition, in virtue of which an individual is affected by several local affections of the same nature, and Trousseau[4] quotes, with approval, a similar definition in the dictionary of Littré and Robin.

1 *Dict. de Méd. et Chir. Prat.*, 1831, vi. 298.
2 *The Pedigree of Disease*, 1884, p. 71.
3 *Leçons de Pathologie expérimentale. Généralités*, p. xiii
4 *Clinical Medicine—New Sydenham Society Translation*, iv. 358.

Chomel,[1] writing in 1856, was more explicit. He defined a diathesis as a disposition in virtue of which several organs, or several points in the economy, are, simultaneously or in succession, the seats of affections, spontaneous in their development and identical in their nature, although they may present themselves under different aspects.

On this side of the Channel such views met with more ready acceptance in Edinburgh than in the London schools. Amongst the Edinburgh professors was Thomas Laycock, a man deeply interested in the constitutional aspects of disease, and who instilled into many of his pupils a share of his own enthusiasm. Amongst these was Jonathan Hutchinson, a man of remarkable ability and immense clinical experience, who exercised a profound influence upon medical thought in London, and indeed over a far wider area. When we recall his oral teaching, or read his writings, we realize how his ideas outstripped the knowledge of his day, and how he fell into errors on that account. In his often quoted lectures, published under the title of 'The Pedigree of Disease', Hutchinson expressed views which were in complete accord with those of Trousseau and Chomel. For him diathesis was 'any condition of prolonged peculiarity of health, giving proclivity to definite forms of disease'. He spoke of it as 'a disease which lasts a lifetime, which may be active at times and latent at times, and which may be handed on to another

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[2] *The Pedigree of Disease*, [illegible]
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miscellaneous collection. Amongst them were infective maladies, such as tuberculosis and leprosy, a number of cutaneous disorders, leukaemia and cyanaemia, oxaluria, phosphaturia and a deficiency disease, scurvy. Obviously theory had quite outstripped fact.

A further development, which had its origin in the French school, was the conception of what might be called the larger diatheses, arthritic, strumous, dartrous and the like, under which headings were grouped sets of maladies, often with little obvious affinity save that they are apt to occur in association.

Of such diatheses arthritism proved the most viable, and has played a large part in the teachings of the French school.

Debove,[1] writing in 1903, acknowledged that the term arthritism, in so common use in France, was little heard beyond her borders, and was wont to surprise foreigners. He described it as embracing things true and things false; and as including a number of maladies which do not involve the joints, but have a certain affinity to gout. Amongst these he mentioned glycosuria, renal colic and obesity. Debove added that the category could be extended indefinitely according to the views of the enumerator.

Mention should be made of another view of arthritism, of which Hanot was an adherent, which looked upon it as an impairment of the power of resistance of the fibrous tissues in general, producing a liability to the

[1] 'Étiologie de la Goutte', *Arch. Gén. de Méd*, 1903, i. 865.

generation'. In another place he wrote of a diathesis as little more than an extremely chronic disease.

Obviously those who held such views had moved far away from the conception of a diathesis as a mere predisposition to a malady. They did not regard it as of necessity an inborn peculiarity, and indeed, both Trousseau and Hutchinson admitted that syphilis fulfilled all the requirements of their definitions.

Although such conceptions made no wide appeal in this country nor indeed outside France, they did in fact constitute a step forward. As Germain Sée wrote: 'La disposition est un mot pour masquer notre ignorance', and the most that can be said for the word predisposition is that it states the fact that some are more liable than others to this or that disease. Trousseau, Chomel, Hutchinson, on their part were feeling their way towards a conception of something much more than a mere word, to that of an underlying state to which the liability is due. Just as W. H. Walshe,[1] another Edinburgh graduate, in a lecture delivered as early as 1855, pictured the diathetic maladies as 'apparently generated and sustained by an intrinsic [illegible] resulting from some perversion of the nutritive processes of the individual'.

Probably no explanation has come nearer to the truth, but many years elapsed before the progress of biochemistry provided it with a firm foundation, and the diathetic diseases [illegible] Walshe [illegible]

[1] Med. Times and Gaz., 1855, [illegible]

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The doctrine of arthritism reached its culminating point with the appearance, in 1882, of Bouchard's well-known book, *Maladies par Ralentissement de la Nutrition.* Not only did Bouchard present, in clearly set out sequence, the arguments in support of the existence of an arthritic diathesis, and the inclusion of certain morbid events under that name, but also he took a long step in advance of his predecessors, in that he was the *first to attempt to explain the association together of the* several members of the arthritic complex by assigning to them a definite, common cause, namely a slackening of the metabolic processes.

and other countries. Nevertheless his fundamental conception proved to be ill-founded, and the progress of biochemistry has taught us that matters are far less simple than he supposed.

The work of Emil Fischer, and his successors, which has revealed the structure of the molecules of the proteins, and similar investigations of the other main constituents of living organisms, together with a better understanding of the metabolic processes of which the tissues are the seats, have taught us that the metabolic processes are carried out step by step. The huge protein molecule is not burnt as a whole, but its component aminoacids are dealt with individually, along different lines, and by specialized enzymes. Only the hormones secreted by certain endocrine glands, and notably by the thyroid, have the power of regulating metabolism as a whole. A general damping down of the metabolic forces may explain some of the phenomena of myxoedema and cretinism, but cannot account for the troubles grouped together by Bouchard under the heading of arthritism.

The doctrines of diathesis occupy a very small place in German medical literature. In 1911 the subject was discussed at a meeting of the Kongress für innere Medizin,[1] and in the course of that discussion Wilhelm His said: 'We understand by diathesis an individual, inborn, and often inherited state, in virtue of which physiological stimuli produce abnormal reactions; and condi-

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Although Bouchard was not the first to suggest an underlying chemical basis of predisposition, he was the first to suggest a chemical defect of a tangible kind, instead of a quite intangible factor behind a group of kindred or apparently kindred maladies. The discovery of uric acid in the blood of gouty people, which opened a new field of clinical chemistry, had been made some thirty years previously, and chemical theories readily suggested themselves in connexion with other diseases.

Bouchard's monograph, which appeared to set the doctrine of arthritism upon so scientific a basis, produced a deep impression at the time of its publication, and his views gained wide acceptance, both in his own

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tions of life which are harmless to the majority of members of the race bring about morbid states.' His added that diatheses differ in degree in different individuals, and at different times, and that their lower limits merge imperceptibly into the normal. Such a *definition approaches very closely to those usually given* of idiosyncrasy, and von Behring, who put forward a similar definition, distinguished diathesis from idiosyncrasy in that the former implies sensitiveness to stimuli of various kinds, whereas the stimulus which evokes an idiosyncrasy is of some one definite kind.

A definition recently put forward by R. J. Ryle[1] supplies a bridge between the older and newer knowledge. Ryle suggests that we should think of a diathesis as 'a transmissible variation in the structure or function of tissues rendering them peculiarly liable to react in a certain way to certain extrinsic stimuli', and adds that 'not all who acquire the disease have the diathesis, but those who have the diathesis are more likely to acquire the disease than those who have not'.

This brings us round full circle to the original notion of a predisposition to a malady.

It was the coming of bacteriology, which supplies in the bacteria definite, concrete agents of disease, attacking the organism from without, that caused interest in diathesis and kindred conceptions to flag. Attention became concentrated upon the seed rather than upon the

1 'Physical Type and Reactions to Disease', *Guy's Hosp. Gaz.*, 1926, xl. 546.

soil, and it was almost forgotten that there are maladies which owe their origin to no such external invaders.

Those inborn factors which must needs be studied at the bedside were relegated to a back place, and received but scanty attention either from teachers or students. The word diathesis, around which so many controversies had centred, was relegated to the dust-heap of obsolete terms. Only here and there a voice crying in the wilderness pleaded for a hearing for the older views.

But it is not in the laboratory alone that scientific work can be carried out, and once again the pendulum, having reached the limit of its swing, has entered upon its return journey. The inborn factors in disease are once more attracting attention, especially in Germany and Austria, but the word constitution has taken the place of diathesis and its contemporary terms. Such works as those of Julius Bauer,[1] very storehouses of information on this subject, bear witness to the depth as well as to the extent of the reawakened interest.

Constitutional Clinics have been established in various centres, notably in New York, Berlin, and Turin, in which valuable investigations are being carried on by anthropometric and other methods.

In our own country the reawakened interest has been less vocal, but the attention which the constitutional aspects of disease are attracting is greater than the

[1] *Die Konstitutionelle Disposition zu inneren Krankheiten*, 3rd ed., 1924. *Vorlesungen uber allgemeine Konstitutions- und Vererbungslehre*, 2nd ed , 1923.

tions of life which are harmless to the majority of members of the race bring about morbid states.' His added that diatheses differ in degree in different individuals, and at different times, and that their lower limits merge imperceptibly into the normal. Such a definition approaches very closely to those usually given of idiosyncrasy, and von Behring, who put forward a similar definition, distinguished diathesis from idiosyncrasy in that the former implies sensitiveness to stimuli of various kinds, whereas the stimulus which evokes an idiosyncrasy is of some one definite kind.

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that of the naturalist who studies man and his disorders from the point of view of biology. This one-sided approach has coloured all the ideas which were advanced, from time to time, concerning constitutional tendencies, temperaments, and diatheses. The ideas which underlay those terms originated, for the most part, in times when many of the concepts of modern science were as yet unformed, when little was known of the laws of heredity, when the theory of evolution had not yet taken form, and when such entities as chromosomes, hormones, vitamins, and antitoxins were not yet dreamed of.

In order that we may get further it will be necessary to re-lay all the foundations of our subject by the light of the newer knowledge. When so doing many cherished notions and some time-honoured terms will have to be discarded, whilst many new facts will need to be taken into account. This is what is being attempted in the constitutional clinics and elsewhere, and it is the purpose of this essay to try to sketch the useful lines of approach to a better understanding of the parts played by inborn factors in connexion with morbid states.

The essay is divided into two parts. In the first section the fundamental studies upon which the reconstructed edifice will need to be built up will be reviewed briefly. Firstly, the meaning of the terms health and disease need to be considered.

Next, the bearing upon medical problems of recent advances of biochemistry will be discussed, and after that the influence of the theory of evolution upon

scantiness of its literature might lead one to suppose. Undoubtedly the interest is growing, and year by year the need to study the part which the patient plays in connexion with his maladies is emphasized by fresh spokesmen, amongst whom A. F. Hurst, J. A. Ryle, Langdon Brown, and Maitland Ramsay [1] call for special mention.

The word constitution has a much wider significance than had diathesis, and predisposition to disease is only one facet of the subject. The constitution of a man is the sum of all his qualities and all his peculiarities. It embraces the colour of his hair and eyes, the shape of his head and limbs and features, his functional peculiarities, physical and chemical, and the mental and psychological features which take so large a part in shaping his relations to his environment. Each and all of these factors have a share in rendering him more or *less* liable to a disease than his fellows. Relative natural immunity is, indeed, no less important than morbid predisposition.

Moreover, the constitution of the patient plays a very important part in *shaping* the diseases from which he suffers. The picture of a malady represents the reaction of the patient, his protest against the attack and his devices for repulsing it.

Until recently the subject has always been approached from the standpoint of the would-be healer rather than

[1] A. F. Hurst, *Brit. Med. Journ.*, 1927, i. 823, 866; J. A. Ryle, loc. cit., sub. 9; W. Langdon Brown, *Brit. Med. Journ.*, 1930, i 525; A. Maitland Ramsay, *Glasgow Medical Journal*, 1927, viii. 65.

cussed, however attractive from the scientific standpoint, have but little bearing upon the practice of medicine, and few important lessons for those whose work lies in the sick-room and hospital ward.

It may even be suggested that although the study of the constitutional aspects of disease has been, to a large extent, relegated to the background during the last half-century, there has been, during that same half-century, an unparalleled advance of both medicine and surgery. But it must not be forgotten that, in so far as those advances are in the field of preventive medicine and aseptic surgery, they are only in a minor degree concerned with inborn factors; for so long as the individual is sheltered from attack, his powers of resistance are not called into play.

Another great line of advance has been the application of laboratory methods to the solution of clinical problems; whereas it is in the ward rather than in the laboratory that the importance of inborn factors is to be appreciated. The clinical worker relies largely upon what may be called his clinical insight; a quality which is purely innate, but which has been developed more and more as the outcome of accumulated experience. The family doctor has watched many of his patients from their birth onwards, and perhaps their parents before them. They trust him because, as they say, 'he knows their constitutions'.

The medical man trains himself or has been trained, by the example of those who taught him, to recognize

medical thought; and finally the bearings upon medical questions of the modern theories of heredity. In the second section an attempt will be made to apply the newer knowledge to the problems presented by individual groups of maladies.

In the first place the relation of disease to physical structure will be considered under two heads, namely, the liability of persons of different builds, features, and general conformations to develop particular maladies, and secondly, the influence of structural anomalies and deviations from type, indirectly predisposing to disease. A chapter will be devoted to that most interesting group of hereditary maladies the tissue defects, or abiotrophies as Gowers called them; some of which do not manifest their presence for years after birth. In another chapter will be discussed the influence of deviations from the average chemical structure and chemical life of the tissues in predisposing to, and shaping the manifestations of, some diseases.

The inborn factors in infective maladies will call for consideration; and lastly the idiosyncrasies, the remarkable sensitivities of some individuals to influences which have no obvious ill effects upon the vast majority of the members of the human race. These range from idiosyncrasies with regard to particular pollens or animal emanations, to grave allergic diseases, such as asthma.

The several conclusions reached and inferences to be drawn, will be summed up in an epilogue.

It may appear to some that the subjects here dis-

PART I

THE BASIC PRINCIPLES OF PRE-DISPOSITION

I

HEALTH AND DISEASE

Men are called healthy in virtue of an inborn capacity to easy resistance to those unhealthy influences that may ordinarily arise; unhealthy in virtue of the lack of that capacity.—ARISTOTLE, *Categoriae*, viii. (trans. Edgehill).

THE living man may be compared to an aviator upon war service, whose safety depends upon a number of different factors. As he flies over the enemy's lines he is a target for shot and shell, is at the mercy of wind and weather; and his life depends upon his own alertness and resource, upon supply of fuel and of oil for lubrication, and upon the efficiency of all parts of his machine. So too we, as we go through life, are assailed by bacteria and protozoa; our well-being is at the mercy of our environment, and depends upon climate and food-supplies. Moreover, if our tissues are not of the first class of their kind, they show, prematurely, signs of wear and tear.

As Aristotle clearly recognized, what we call health is no mere quiescent state, but a condition of unstable equilibrium, maintained by a continual struggle. His definition, with its so modern ring, has much in com-

the qualities and individual needs of his patients. He realizes that each is an individual, and not merely a member of the human race. The task of the practitioner is far more than to apply the knowledge supplied to him from the laboratories; he does not merely ask himself, or look to his text-books to tell him, what is good for pneumonia, but calls upon his experience to guide him as to how he may best help the particular patient to come through his attack of pneumonia with the least possible damage.

Wittingly or unwittingly, the practitioner of medicine is constantly engaged in the study of constitutions and *predispositions, and of reactions to environment.* He must, throughout his active life, be a student of the inborn as well as of the external factors in disease.

continuous, normal, nutritive mutation and renewal of the bodily tissues.'

Nevertheless, teachers of medicine and authors of text-books still find themselves obliged to treat, in sequence, of series of discrepant pictures called diseases; as if maladies were all of a kind, and capable of being classified into systematic groupings, corresponding to the genera and species of plants and animals.

How else, indeed, could they present their subject to their hearers and readers? As Wilhelm His [1] pointed out in a recent Rectorial Address, many morbid pictures recur over and over again with only trifling variations, and to disregard such groupings would result in chaos. Nevertheless, the morbid pictures must not be looked upon as occupying rigidly defined compartments, but rather as merging into each other.

Even if an attempt be made to reach a more scientific classification of diseases by grouping together all the effects of invasion of the organism by some special bacterion such as the tubercle bacillus—a method for which there is much to be said from the standpoint of the bacteriologist—from the standpoint of the clinical worker nothing will be gained by the association, under a single heading, of pictures so widely different as those of pulmonary tuberculosis, tuberculous meningitis, spinal caries, and Addison's disease.

There are similar objections to the assembling, under one heading, of all the morbid effects of the continued

[1] *Ueber die natürliche Ungleichheit der Menschen.* Berlin, 1928.

mon with some of the most recent definitions of health and disease. Thus, George Draper,[1] in his book on *The Human Constitution*, defines disease as 'the expression of the reaction between a complex set of external agents and an equally complex organism striving to survive in the midst of them', and F. W. Andrewes,[2] who speaks of the healthy body as not only perfectly adjusted to its surroundings, but capable of adjusting itself, within reasonable limits, to a rapidly changing environment, defines disease as a condition in which the body has fallen, in greater or less degree, out of harmony with its surroundings.

Still more recently, H. D. Rolleston[3] spoke of disease as 'the mental picture of the manifest reactions of a living organism in response to harmful factors, whether derived from outside the body or arising internally'.

These recent definitions all avoid the error against which that great teacher, Thomas Watson,[4] warned his hearers, in a lecture delivered almost a century ago. He bade them avoid 'the strange mistake, too often made or imputed, of regarding disease as a thing, or (as the phrase goes) a "separate entity" by which the body is possessed and damaged—something which can be contemplated as apart from the body, which it may invade'. Watson added that, 'for the most part, disease consists in some derangement, suspension or perversion of the

[1] *Human Constitution*, 1924, p. 222.
[2] *Lancet*, 1926, i. 1075. [3] *Brit Med. Journ.*, 1929, i. 281.
[4] *Lectures on the Principles and Practice of Physic*, 5th ed., 1871, i. 6.

ternal factors. Sometimes the one and sometimes the other is the more conspicuous.

Each one of us is exposed, during every day of his life, to unhealthy influences to which he has some inborn capacity of resistance, but the degree of that capacity varies widely, even amongst individuals who pass as healthy. It is, moreover, a discriminative capacity, different individuals being resistent to different kinds of attack.

On the other hand, there are many of us who possess latent defects of structure or function, inborn and for the most part inherited, which are apt to be revealed, sooner or later, by the effects produced by external influences which are innocuous to the average man. Upon some of the subjects of such defects slight injuries, upon others exposure to bright light or to extremes of temperature, exert a deleterious action. For some individuals those trifling traumata which go to make up the wear and tear of daily life, are apparently the provoking causes of grave disorders.

As the pictures upon the walls of an art gallery are by a variety of artists and of widely different kinds; some portraits, others landscapes, others again subject pictures, and some studies of still life; so the clinical pictures which we call diseases differ markedly amongst themselves, and are indeed the products of different kinds of processes. Nevertheless, some of them fall into groups which have much in common. Of such groups the infectious fevers offer the most obvious examples; they form a natural family of maladies.

administration of such a poison as lead or alcohol. The clinical pictures of the gastro-intestinal, cerebral, and peripheral-neuritic effects of lead poisoning, and that of saturnine gout, differ so widely amongst themselves, that if they were not known to have a common origin they would be looked upon as distinct maladies.

Indeed, the symptom-complexes which we call diseases have, for the most part, little in common beyond the facts that they constitute departures from the average standard of health, and tend to bring about, sooner or later, conditions incompatible with the survival of their subjects. These two aspects lie behind the various designations of disease. The Greek and Latin terms *νόσος* and *morbus* convey the idea of fatality, whereas the more modern terms such as ailment, illness, *maladie*, and the word disease itself, point rather to the discomfort entailed than to danger to life.

So greatly have our notions regarding disease been influenced by the progress of bacteriology, and by all that that science has taught us, that we are in danger of forgetting that not all maladies have their origin outside the body, nor are due to invasion by bacterion, protozoon or virus. The man plays a very important part in connexion with his diseases, and to quote Hippocrates:[1] 'As to the manner of diseases, upon inquiry it will be found, that some are born with us.'

Indeed in all diseases there are both internal and ex-

[1] *De Humoribus*, § 12. (*Hippocrates: Upon Air, Water and Situation*, trans. by Francis Clifton, 1734, p. 41.)

mechanism remains well under control, and the temperature does not rise to a level which is gravely deleterious to the tissues. To quote Andrewes[1] once more, a bacterial infection does not always give rise to morbid happenings, as the symptom-free carriers of pathogenic bacteria show, only when the body begins to defend itself against attack does trouble arise: 'It is an evil that a tissue should become inflamed and that the body temperature should rise in an acute infection; but it is a lesser evil than that the infecting agent should overrun the body unchecked by any antagonistic mechanism.'

Individual cases of any particular disease, infective or other, are not exactly alike, as are the prints pulled from a lithographic block; they resemble rather the drawings made from the same model by individual members of a drawing class. The differences between one case and another are often very slight, but they are familiar to all who practise medicine. By no means all such differences are due to the constitutional peculiarities of the patients; in the infective maladies, as has been mentioned, the virulence of the pathogenic organism plays an important part, and the clinical picture presented may be modified profoundly by the severity and distribution of local lesions resulting from the disease.

On the other hand, factors inherent in the patient undoubtedly play important parts in modifying the syndrome observed; as is witnessed by the conspicuous

[1] Loc. cit., sub 2.

In the infective diseases a morbific agent, a bacterion, a virus, or a protozoon, enters the body from without, and in so doing gives rise to trouble. In such cases the external factor is something concrete, which may be studied outside the body; but daily experience teaches that there are also internal factors at work, *that there is such a thing as a natural liability to*, and a natural immunity against infective diseases. Moreover, it is the human subject rather than the specific micro-organism which shapes the syndromes or clinical pictures by which such diseases are recognized; although a similar response follows a specific bacterial infection in different subjects. The severity of the attack, although in part controlled by the virulence of the invading germ, is also a measure of the resisting power of the organism, its natural or acquired immunity; in other words by the efficiency of its defensive mechanisms.

If we could watch from the air the landing of a hostile force upon our shores, we should witness the disturbances thereby induced in the invaded area, the mustering of troops for the defence, and the evacuation of the inhabitants. These operations, which would fill the forefront of the picture, would represent the reaction of the people attacked. So also, in the case of an acute infection, the clinical picture shows the marshalling and *organization of the defence of the body*.

Even fever may be regarded as a beneficial rather than a harmful process, so long as the thermotaxic

supplies from without must experience serious troubles if any of those supplies are withheld; as witness the phenomena of anoxaemia, culminating in suffocation, and those of starvation of various degrees; but in the diseases under discussion the dietetic errors are much more subtle. The vitamins, which might be described as exogenous hormones, cannot be reckoned as foodstuffs, but exert a profound influence over nutrition.

The vitamin C, which is soluble in water, is contained in foods which avert or cure scurvy; and when it is lacking the tissues are rendered unduly vulnerable to slight injuries, and injuries, slight or severe, play the chief parts in determining the occurrence and distribution of haemorrhages in scorbutic subjects. In the same way the fat-soluble vitamin D is concerned with bone and tooth formation, and lack of it induces rickets; but as is now known, the organism is not wholly dependent upon supplies of that vitamin from without; for it can be formed from ergosterol in the skin, by irradiation with light or ultra violet rays.

As to the influence of personal factors in deficiency diseases, clinical evidence, and especially that derived from work in children's hospitals, suggests strongly that some individuals are much better able than others to carry on despite shortages of vitamins.

That some infants develop scurvy upon diets which others can take with impunity, or even upon a diet which appears hardly open to criticism, is a matter of

differences between cases of the same infective malady in children and adults respectively. No better example can be quoted than that of rheumatic fever. In the child the greater frequency and severity of the cardiac accidents, and the frequency of chorea and nodules, together with the comparative insignificance of the articular lesions, which are so conspicuous in adults, give to the syndrome a special stamp. As other instances may be cited the different distribution of the local manifestations of tuberculous and pneumococcal infections in children and adults respectively. The influence of sex is much less obvious; but apart from obvious examples of sex-linked inheritance, there is evidence of relative immunities and liabilities in males and females respectively. Draper,[1] in a recent book gives statistics of the incidence of diseases in the two sexes, for many of which no obvious explanation offers itself. We do not know why pneumonia should be much commoner in males, and purpura haemorrhagica in females. Some such differences may be ascribable to occupations, and some to secondary sexual causes.

Another well-defined group of maladies, widely different in their outer aspects, but akin in their origins, are the so-called deficiency diseases. In them instead of an invading micro-organism the main external cause is lack of a vitamin; if indeed a negative factor can properly be described as an external cause.

It is inevitable that an organism which depends upon

[1] *Disease and the Man*, 1930, p. 108 et seq.

animal. The internal factors, on the other hand, are conspicuous, and that, in many cases at least, the hypersensitivity is inborn is shown by its appearance in successive generations of a family.

Athwart such lines of classification runs a system of grouping of diseases according to the organs or parts which they affect, and with such groupings neither medical teachers nor writers have been able to dispense. A peculiarly interesting group of such syndromes is that resulting from lesions of the endocrine glands. Just as the several glands have widely different functions, the syndromes which result from suppression of their functions, or from excessive secretion of their hormones, are of diverse kinds. No more clearly defined diseases exist than exophthalmic goitre and myxoedema, acromegaly and Addison's disease; but seeing that the functional derangement may be of any degree, the text-book descriptions of these maladies are obviously based upon extreme examples. There are all grades of hypo- and hyper-thyroidism. Although in most instances the underlying morbid process in an endocrine disease is of the same nature, as in the case of the adrenal lesions of Addison's disease, which are almost always tuberculous, there is no necessary connexion between the syndrome due to error of glandular function and the nature of the glandular lesions.

There is an obvious analogy between the maladies due to lack of a hormone, and the deficiency diseases, but the analogy must not be pressed too far. L. J.

common experience, whereas other infants appear to be relatively immune. McCarrison,[1] who bases his opinion mainly upon experimental feeding of animals, speaks confidently of the existence of individual predispositions to deficiency diseases. He holds that 'the quantities of vitamins necessary for the harmonious regulation of the metabolic processes vary with the individual and his rate of metabolism'. Moreover, he found that different organs of the body have their individual liabilities, as also has the same organ in different individuals, and concluded that 'idiosyncrasy, whether of individual subjects or of individual organs, is an important factor in determining the onset and the manifestations of deficiency disease'. That the stage of development of the patient's tissues plays an important part in shaping the clinical picture, is evidenced by the difference between infantile scurvy with its subperiosteal haemorrhages, and the same malady as met with in adults.

In a third group might be included what may be called the allergic diseases, such as asthma, at least in some of its forms, and angio-neurotic oedema; but this group is not clearly defined, for allergic phenomena play conspicuous parts in a variety of maladies, including the exanthemata. The external cause often appears quite inadequate to bring about such striking results as are seen, in not a few cases, to follow the inhalation of the pollen of grass or the exhalation of a particular kind of

[1] *Studies in Deficiency Disease*, 1921, p. 40.

the early extension and later contraction of the paralysis produced by poliomyelitis.

It is obvious that many different factors are concerned in the production of the various morbid pictures which differ so widely in their characters; and that the factors which predispose an individual to one malady may be wholly different from those which predispose him to another. Nor is it to be wondered at that no satisfactory system of classification of diseases has been evolved, seeing that the items to be classified are, in many instances, not really comparable; as Thomas Watson said, they are not entities.

Nor is it to be wondered at that wholly different views have been, and are, entertained as to what is entitled to be called the cause of a disease, and these differences of opinion extend even to the infective maladies. Whereas to some it appears obvious that the cause of such a malady is the infecting organism, and around this tenet modern medicine has, to a large extent, taken shape, there are others who maintain that the cause of pneumonia is not the pneumococcus, but rather a state of the tissues of the individual infected, which brings about a response of a characteristic kind to the specific invasion.

Those who are interested in such discussions will find the conflicting views, and the arguments upon which they rest, ably set out in the writings of Lubarsch, Julius Bauer, F. Kraus, Hueppe and Martius[1] amongst

[1] Lubarsch, *Deut. med. Wchnschr.*, 1922, xlviii 787, 1025; Bauer, J.,

Harris and T. Moore[1] have brought forward some evidence of the existence of a vitamin balance comparable to the balance of the endocrine glands which constitutes the great regulator mechanism of the bodily processes.

More crude effects are produced in a variety of morbid conditions, by pressure on ducts of such glands as the liver or pancreas, or upon neighbouring blood-vessels or nerve-trunks. As an example may be cited the often-repeated clinical picture of carcinoma of the head of the pancreas.

A large and most characteristic group of morbid pictures is provided by the diseases of the nervous system. From such pictures the skilled neurologist can often localize with accuracy the seats of lesions of the brain or spinal cord, and experience often enables him to deduce the nature of the lesion to which the syndrome is due. No more striking example of such a syndrome can be quoted than that of tabes dorsalis, which is now known to be a manifestation of syphilitic infection.

Amongst nervous diseases there are some which are strongly hereditary, but in which there is little evidence of the working of any external causative factor. Of such pseudo-hypertrophic muscular dystrophy offers a good example.

The syndrome due to a local lesion will obviously vary according to the extent of the lesion; as is seen in

[1] Harris and Moore, *Biochemical Journal*, 1929, xxiii. 114.

ments, there are internal and external factors concerned of such minor degrees that their presence is hardly recognizable, or fails to be detected by the methods at our disposal.

II

THE CHEMICAL BASIS OF INDIVIDUALITY

The particular chemical type, the particular mode and rate of the chemical changes of tissues, passes from father to son, as the shape of the features passes.—JOHN SIMON. 1876.

IN the preceding sketch of the history of the doctrines of diathesis it was mentioned that, as far back as the middle of the nineteenth century, some writers had suggested that the liabilities of certain individuals to particular diseases might have their origin in disturbances or irregularities of the metabolic processes of the individuals in question. At that time such an explanation was open to the objection that it explained the unknown by the even less known; but although biochemistry has made immense advances since then, the further the matter is investigated the more probable does it appear that the suggestion is justified.

It will be desirable therefore to examine, in this section, the evidence which favours the supposition that our individuality has a chemical basis; for the inborn factors in disease are merely facets of our individuality.

In our pursuit of this aim it will be necessary to go back as far as the very germinal cells and their chromo-

others. To some of us it will seem that the disputants are beating the air; that there is right upon both sides, and that both are wrong if they claim that any single factor is entitled to be spoken of as *the cause* of any malady. We may hold, with Lubarsch, that it is misleading to assert that the tubercle bacillus is the cause of tuberculosis, and may prefer to say that the entry into, and multiplication of tubercle bacilli in a predisposed body is the cause of that disease.

The two factors, the soil and the seed, the external and the internal, must both be taken into account if we are to form any adequate conception of the nature and causation of any disease. The relative importance and prominence of the two factors vary very widely; but whilst on the other hand, the constitutional factor cannot safely be ignored when discussing the causation of pneumonia, it is equally necessary not to leave out of account, when discussing the causation of haemophilia, the slight injury which may have started a fatal haemorrhage.

It is permissible to suppose that, as in the production of those wider departures from the standard of health which receive the name of diseases, both internal and external factors are at work, so also in the causation of those lesser departures, which it is difficult to name or classify, and which may be spoken of as trifling ail-

Die konstitutionelle Disposition zu inneren Krankheiten, 3rd ed., 1924; Kraus, F., *Die allgemeine und spezielle Pathologie der Person*, 1919; Martius, F., *Deut. med. Wchnschr.*, 1918, xliv. 449, 481.

and substances of the lecithin group, which last, being insoluble in water, are the more valuable factors in cell life, there is room for immense variety and for differences not only between species and genera, but also between individuals of a species. In the living organism everything is in flux, there is action everywhere, in the limbs, circulation, and viscera; in the constituent cells of the tissues, in the molecules concerned in the metabolic processes, and even within the very atoms of which the molecules are composed. Every individual differs from every other, there is no rigid line between species and species; no fixed standard of normality and health.

It can hardly be wondered at that, in such an atmosphere of change, numbers of variations from the average occur, nor that some of these are so pronounced as to become conspicuous. It would be more wonderful if it were not so. The departures from the average of the species may be peculiarities either of structure or of function, and there is good reason to believe that even structural diversities have chemical origins.

Mutations, those step-like variations which originate in the germinal cells and are transmissible from generation to generation, may be no more than slight deviations from the average, or may be so conspicuous as to justify their description as occurring *per saltum*. In this connexion Goodrich[1] pictures what happens to a molecule when an atom or an atomic grouping is removed from it, as suggestive of what may occur in the factors of

[1] *Living Organisms*, Oxford, 1924, pp. 85 and 95.

somes, into which, in the words of J. B. Leathes,[1] 'were packed, from the beginning, all that pertains, if not to our fate and fortunes, at least to our bodily characteristics, down to the colour of our eyelashes'.

It is hardly possible to imagine the concentration of so many potentialities into structures so minute, unless *we suppose that the underlying factors of the various* future developments are inherent in the molecules of which the chromosomes are built up. Huxley[2] realized this when he wrote, as long ago as in 1875, that 'to be a teleologist and yet accept evolution it is only necessary to suppose that the original plan was sketched out, that the purpose was foreshadowed, in the molecular arrangements out of which the animals have come'.

In his illuminating Rectorial Address, delivered in Prague in 1896, Huppert[3] argued that chemical differences in the constituents of the germ-cells must determine the attributes of the organisms developed from them. He was one of the first to point out the differences of chemical structure and chemical life of animals of different species; and from such differences he deduced the existence of similar differences in the materials composing the germ-cells from which they spring.

In such a congeries of molecules as a germ-cell, made up, to a large extent, of proteins, nucleoproteins,

[1] *British Assoc. Oxford Report*, 1926. Sect. I, Physiology. Presidential Address, p. 208.

[2] *Life and Letters*, 1900, i. 456.

[3] *Die Erhaltung der Arteigenschaften.* Prague, 1896.

essential oils to which their scents are due. In the animal world they are borne witness to by specific colourings, by protective secreta, odorous or concealing, less obviously by specific differences of haemoglobins of bile-salts, and of the tissue proteins as revealed by the precipitin test.

Nor can it be doubted that similar, but much more subtle differences than those which distinguish species from species obtain even within the boundaries of the species. Were it not so it would be necessary to picture the existence of specific barriers too rigid to be compatible with the evolution of living forms.

Moreover, there is clear evidence that such differences do actually exist. Some deviations from the chemical type of a species are wide enough to compel attention, such as albinism and certain chemical malformations which will be discussed in a later chapter. Others less conspicuous doubtless escape notice; and others again, still more subtle although often more conspicuous, such as idiosyncrasies to foods and pollens, are still beyond the reach of chemical methods.

Of the differences of this latter class are the remarkable differences in the behaviour of blood when introduced into the circulation of another member of the same species. These phenomena, which are of great practical importance in the practice of transfusion, have attracted much attention in recent years. The blood of human subjects is classed under certain groups according to its behaviour in such circumstances, and the

inheritance when a mutation appears. Lenz[1] carries the conception of molecular mutations a step further, and suggests that on any chemico-physical conception of the germ-plasm it is not to be expected that it will be the seat of smooth and continuous change, but rather that it will be altered in successive *steps*, by the removal, or by shifting of the positions of molecular groupings.

One is tempted to venture yet one step further, and to point out that, since in the experimental breeding of *Drosophila* the same mutation is seen to originate over and over again in the species, such a happening may be compared to a chemical reaction in the laboratory, which is repeated as often as the necessary conditions are reproduced.

It is hardly necessary any longer to argue in support of the view that the various genera and species of plants and animals differ in their chemical structure. Not only do we recognize the facts that the fat of a sheep differs in its composition from that of a pig, and that the proteins of an animal of one species act as foreign proteins to animals of another species, but it is also evident that the members of different species differ in what may be called their chemical lives, in that complex of chemical happenings to which we give the name of metabolism.

In the vegetable world such differences are manifested in the pigments of leaves and flowers and the

[1] *Handbuch der normalen und pathologischen Physiologie*, 1926, xvii.

The number of possible groupings of the several fractions, in which each fraction is represented only once, is very great indeed, and when it is considered that the proportions of individual amino-acids vary widely and that one or more may be missing from the molecule of any individual protein, it is obvious that the possible combinations and groupings must exceed in numbers even the figures with which astronomers have to deal.

It cannot be doubted that natural selection works through chemical as well as structural modifications, nor that the features in which an organism differs from type are foreshadowed in the molecular complexes of the chromosomes.

In an address delivered in 1926, J. B. Leathes[1] pointed out that all which needs to be premised in order that the whole course of evolution may follow, is the disposition of matter in molecules or aggregates which shall be unstable and immensely variable; and that such matter shall have and retain the power to determine the deposition of other matter in conformity with its own pattern, or with patterns which enable it to exercise such power.

It may be supposed that, as evolution has proceeded, organisms have been produced which differ in chemical structure, as well as in their forms, until the proteins of a group of living things have become so far differentiated that they behave as foreign proteins towards members

[1] Loc cit, sub. 1.

agglutination of the red corpuscles when donor and recipient belong to incompatible groups is attributed to the presence or absence of as yet intangible substances known as agglutinogens and agglutinins.

That membership of the several blood-groups is transmitted from parent to child appears to be well established, and it is suggested that the inheritance follows Mendelian lines. But the groups would appear to represent racial quite as much as individual differences; as would appear from work done upon various races. It would seem that the group known as A is present in higher percentage in the races of Western Europe, and that the percentage of group B tends to increase from west to east.

There is still much to be learned concerning the blood-groups, but it can hardly be doubted that they testify to chemical or physico-chemical differences within the boundaries of the species.

It is the extreme complexity of the molecules of the proteins, which are the essential constituents of all living tissues, that makes it possible to imagine how chemical individuality can exist. Their huge molecules are built up of some twenty or more fractions, each an individual compound, which, being an amino-acid, is capable of acting as an acid and also as a base. To its neighbour on the one side it acts as an acid, to its neighbour on the other side as a base, and so the several constituent fractions are able to hold hands, so to speak, and to form chains and clusters.

a destroyed organ cannot be reproduced, nor a lost limb replaced.

A lizard may grow a new tail of a sort, but in a man who has lost one kidney, the remaining kidney has to enlarge and do the work of two.

Only the germinal cells retain the power to reproduce all the tissues and all the structures of the original organism, and it is in virtue of that power that the reproduction and survival of the species is committed to them. Whatever may happen to the somatic cells affects the individual involved, but not the future of the race. Just as in a bee community the worker bees are specialized for the performance of their appointed tasks, and minister to the fertile queen and her progeny, but have no further share in the propagation of the race, so the somatic cells are specialized to wait upon the needs of the germ-plasm.

Yet the germ-cells are composed of the same kind of materials as the somatic, and although protected from many kinds of injury to which the body-cells are liable they are no more immortal than they. The main difference is that they retain the totipotentiality which the somatic cells have lost. In what that totipotentiality consists we do not know.

There are indications that the germ cells may be altered by certain agencies, such as exposure to X-rays, and that thereby the progeny may be affected; but it is commonly held that to the germinal cells alone is due the transmission of the forms and functional charac-

even of kindred groups. When that stage has been reached interbreeding will no longer be possible, the species will have been established, and thenceforward its main characteristics will be maintained.

Evidently, as the organism becomes more elaborated there will be ever increasing opportunities of departure from type. As Andrewes puts it, 'a chronometer can suffer from a greater variety of defects than an hour-glass'.

The simpler organisms possess a great power of repairing damaged tissues, but, as evolution proceeds from the single cell to the nations of cells which constitute the higher plants and animals, the somatic cells of which their various tissues are built up become specialized for the particular purposes which they are called upon to serve; some to form the skeleton and others muscles; some to produce external and internal secretions, others to ensure the removal of waste materials. In becoming thus specialized the cells lose a part at first, and ultimately almost the whole of their totipotentiality, that power which the primary cells possessed of reconstructing lost parts, and of the more delicate kinds of tissue repair. Such repairs as are still possible are carried out by the wandering cells of the mesenchyme. The reunion of a broken bone, the scarring of an abraded surface, the healing of a wound are still possible even for the most highly developed organisms, and hypertrophy or hyperplasia may compensate for loss of a part, but in the higher animals

variations which diminish liability to disease, than to such as favour its development. Moreover, as is remarked by J. B. S. Haldane and Julian Huxley,[1] in a book published recently: 'Mutations most easily detected will usually be those with large and striking effects; and a large change will be likely to throw the animal's organization out of gear. Mutations of small amount which do not throw the machinery out of gear but may even improve it, must also be occurring, but the smaller they are the more difficult will they be to detect.' In other words, the better the adaptation to the environment, the less likely is any change to be for the better.

A new departure may be, at the same time, both beneficial and harmful, but if the good outweighs the evil it will persist. Thus, when man adopted the erect posture he gave up the hammock-like support of the abdominal viscera, which is a fundamental part of the vertebral plan; and in so doing laid himself open to a variety of minor ills, varicose veins, herniae, and the like; but the gain was far greater than the loss, for it was no less than the mastery of animal nature upon this planet.

It may appear, at first sight, that in this discussion of the basis of individuality an essential difference between variations of form and those of function has been ignored. But, as a matter of fact, the difference is rather apparent than real.

[1] *Animal Biology*, 1927, p. 221.

teristics of the individuals; and if so, we must look to them for the basis of the inborn factors in disease. Each one of us, and each departure from type which he exhibits, may be looked upon as one of Nature's experiments, and the experiment may result in success or failure.

Speaking in 1881, Huxley[1] referring to the normal and typical characteristics of a species said: 'Outside the range of these conditions, the normal course of the cycle of vital phenomena is disturbed; abnormal structure makes its appearance, or the proper character and mutual adjustment of the functions cease to be preserved. The extent and the importance of these deviations from the typical life may vary indefinitely. They may have no noticeable influence on the general well-being of the economy, or they may favour it. On the other hand, they may be of such a nature as to impede the activities of the organism, or even to involve its destruction.'

It is important to bear in mind, in any discussion of constitutional liability to disease, the three possibilities mentioned by Huxley. When approaching the subject from the medical side one is liable to forget the reverse of the picture, the modifications or mutations which are beneficial to the organism. Inborn immunity is no less real than inborn liability to disease. Were there no favourable variations there could be no evolutionary advance. Yet, as will be shown later, it is far more difficult to point to definite examples of favourable

[1] *Internat. Med. Congr. Trans.*, 1881, i. 91.

variations which diminish liability to disease, than to such as favour its development. Moreover, as is remarked by J. B. S. Haldane and Julian Huxley,[1] in a book published recently: 'Mutations most easily detected will usually be those with large and striking effects; and a large change will be likely to throw the animal's organization out of gear. Mutations of small amount which do not throw the machinery out of gear but may even improve it, must also be occurring, but the smaller they are the more difficult will they be to detect.' In other words, the better the adaptation to the environment, the less likely is any change to be for the better.

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[1] *Animal Biology*, 1927, p 221.

If we are justified in assuming that the representation in the chromosomes of the characteristics of the organism which shall spring from them has a molecular basis, differences of form must themselves have been determined by molecular grouping, in other words, must have a chemical origin.

That chemical factors play a conspicuous part in determining bodily form has been revealed by the study of the endocrine glands and of the hormones which they secrete, two at least of which hormones already take their places amongst known crystalline chemical compounds. It is now generally recognized that the endocrine glands constitute a system of balanced regulators, which control many of the most important processes in the animal body, and through its functions tend to shape its structure. By this balanced control, height and weight, slimness and obesity, and also temperature of the body and blood pressure are kept within the not too narrow limits of what is called normality. But, as in a tug of war there is a swaying to and fro; so, within the bounds of the average, there are many opportunities for variations both small and great.

Not a few writers, notably Keith[1] in this country, L. Bolk[2] in Holland, and Pende[3] in Italy, have emphasized the importance of the role played by the endrocrine glands in connexion with the evolution of the

[1] *Huxley Memorial Lecture Nature*, 1923, cxii. 257.

[2] *Lancet*, 1921, ii. 588.

[3] *Constitutional Inadequacies* (trans.), 1928.

races of mankind, but undoubtedly other influences also are at work. The hormones are essentially regulative rather than inventive. They are fully competent to bring about abnormal stature or hirsuties, but we cannot attribute to them extra digits, nor such other eminently hereditary deformities as claw hand, and must look elsewhere also for the causes of malformations by defect, of structural jobs left unfinished, such as cleft palate and spina bifida.

On the other hand, it can hardly be doubted that the endocrine system plays a most important part in the production of those individual and racial differences of form and feature which are revealed by anthropometry, and of which the association with morbid liabilities, of various kinds, is being studied assiduously in an increasing number of Constitutional Clinics.

Following a completely different line of thought, J. B. Leathes[1] adduces the influence of function, of stress and strain for instance, upon the development of connective tissues. He sees in such influences the exciting causes of a secretion of collagen by certain cells of the connective tissues, and the resultant formation of what may be called a fibrous rigging along the direction of the pull, that is to say of tendons and ligaments. To similar influences may be ascribed the structure of the bones, the distribution of the trabeculae in such a way as to meet the mechanical strain to which the bones are habitually subjected.

[1] Loc. cit, sub. (1).

Starting with such a conception of chemical specificity and chemical individuality as has been sketched out in this chapter, it is not difficult to conceive of the handing down, from parent to child, of those peculiarities of form and function which depend upon the chemical structure of the chromosomes. Nor is it difficult to suppose that natural selection works, through the medium of the mutations which occur and recur from time to time, for the better adaptation of the individual, and through the individual of the race, to the environment in which he lives.

Among the legacies thus handed down from one generation to another are predispositions to certain diseases, or exceptional powers of resistance, which play and have played no unimportant parts in the evolution of the human race.

III

EVOLUTION AND DISEASE

Of all the teeth in the terrible comb with which Nature sorts out the inefficient, disease is one of the most formidable.—F. W. ANDREWES. 1926.

SINCE the days when the older notions of diatheses took form the whole outlook upon biological problems, has been profoundly changed by the general acceptance of the theory of evolution; an acceptance which is not impaired by the diversity of views which still persists, as to the mode in which the evolution of living things has come about.

There are, to-day, those who hold that the part played by natural selection has been far less than Darwin supposed, and some who believe that the influence of that factor is almost negligible; despite the fact that when once conceived of, the survival of the fittest is seen to be inevitable. The controversy as to the hereditability of acquired characters still persists, involving, as it does, the vulnerability of the germ-plasm. The views of Lamarck in modified form, the so-called neo-Lamarckism, have not a few adherents.

Whatever views may be held upon such points, the fact remains that in no discussion of the inborn factors in disease can the evolution of the agents of disease, on the one hand, and that of the methods of defence of the organism, on the other hand, be left out of account.

As to what constitutes fitness to survive, man and Nature do not see eye to eye. As civilization has advanced the protection of the sick and weak as also of those whose mental development gives them but a poor chance in the struggle for existence has become more and more developed. The whole aim of medical art, whether therapeutic or preventive, has been to counteract the laws of Nature. We certainly would not have it otherwise, and indeed the highest achievements of human thought and of art, are not unfrequently the work of men who are little fitted for the rough and tumble of a life of struggle.

The part played by disease as an agent of evolution, has no doubt been greater in the case of man than of

the lower animals whose lives are in jeopardy every hour, and of civilized man than of his predecessors the prehistoric cave-dwellers. Our early forebears, although exposed to the far more rigorous climate of an ice-age, and lacking the protections which we regard as essential, probably needed such protections less than we do; but they were constantly exposed to the attacks of wild animals against which their weapons were not wholly adequate, and to the assaults of kindred marauding tribes. They had not much opportunity of being sick.

Modern man, on the other hand, leading a far more sheltered life, and perhaps because he does so, is much more likely to succumb to disease—to die in his bed, as the saying is—and he owes his survival far more to the devices of his brain than to the vigour of his arm. Whether, with advance of preventive medicine and hygiene, on the one hand, and the multiplication of motor vehicles on the other, this situation will again become reversed, remains to be seen.

We are apt to forget how closely, as evolution has proceeded, man has become adapted to the calls upon him. The very possibility of protoplasmic life is limited by the effects of temperature upon proteins, and the range is not a wide one, but man is adapted, not only to temperature, but also to the force of gravity at the surface of this planet, to the pressure of the atmosphere and the blending of its constituent gases, to the character and composition of the available foodstuffs. It is not

to be wondered at that a deviation from the average on his part is apt to place him at a disadvantage.

On the other hand the normal man is able to adapt himself, in virtue of his regulating mechanisms, to considerable changes in his environment. An obvious example of this is afforded by the survival and well-being of races and individuals, in the tropics or in the polar regions, at the sea-level or on mountain sides, without any conspicuous variation of body temperature.

The relation of evolution to disease has occupied the attention of a number of writers in recent years. Of those, in this country, who have contributed to the discussion the names of G. Adami,[1] F. W. Andrewes,[2] Archdall Reid,[3] and W. J. Collins[4] call for special mention.

In later chapters it will be necessary to speak, in some detail, of special aspects of the subject; here it will suffice to review briefly some of its general aspects.

These fall under three chief headings: In the first place, the means of defence of the organism against attacks from without has obviously been improved by the evolution of ingenious defensive mechanisms. Secondly, in the case of infective maladies the invading organism, whether bacterion or protozoon, has developed improved methods of attack as time has gone on, as was well brought out by Andrewes in his Linacre

[1] *Medical Contributions to the Study of Evolution*, 1918.

[2] 'Linacre Lecture. Disease in the Light of Evolution', *Lancet*, 1926, i. 1075

[3] *Present Evolution of Man*, 1896. [4] *Lancet*, 1920, i. 1059.

Lecture. Thirdly, there can be no question that disease has played, and is playing, a very important part as an instrument of natural selection.

Against maladies which have their origin outside the body, in the introduction into it of protozoa, bacteria, or those still mysterious agents known as filter-passing viruses, and against such diseases as result from administration of poisons of various kinds, there have been evolved protective mechanisms of conspicuous efficiency.

The chemical poisons may be considered first, for they provide the simplest examples, in which fairly simple chemical processes are concerned. The simplest example of all it provided by the measures to counteract acid poisons. The neutralization of the acid by ammonia diverted from metabolism, which has the great merit of sparing the fixed alkalies of the tissues, has been developed in carnivorous animals, including man, but not apparently in herbivora, which having abundance of alkali in their food, are little exposed to acid-poisoning. Another simple, but highly important protective device is the combining of toxic aromatic compounds with sulphates, to form the innocuous aromatic sulphates which are excreted by the kidneys: or with glycine to form the acids of the hippuric group. It appears that only in the case of normal aromatic products of the body chemistry, tyrosin, phenyl-alanin, and tryptophane can the benzene ring be broken in the course of metabolism.

However, it must not be assumed too readily that such mechanisms have been evolved in all cases. It is highly probable that in some instances we have to deal with an unrehearsed chemical reaction. When Baumann administered brom-benzine to a dog the animal excreted a derivative of cystin to which he gave the name of a mercapturic acid. The same happens with all dogs and with other halogen-benzines. Yet it is unlikely that before Baumann's experiment any dog had taken brom-benzine. The mechanism was ready to hand, although the contingency could hardly have been prepared for; just as the organic chemist succeeds in preparing synthetically compounds which have never previously existed, but which assume their correct crystalline form, and exhibit predicted properties. Yet in studying such mechanisms we get a glimpse, behind the scenes, of what may be the inner meaning of what is spoken of as predisposition to disease.

Turning now to the infective maladies, the protective mechanisms are undoubtedly much more elaborate. The agents of defence are not yet known as definite chemical compounds, but are revealed to us only by single properties. Such are the antitoxins, agglutinins, opsinins, and the like. They are not yet accessible by the ordinary methods of the chemical laboratory. In many instances they are apparently not present in the organism until it is attacked from without, but once acquired they may remain as long-lasting assets of their possessors. Some of them have the power of slaying

the invaders, whereas others serve as antidotes to their toxic products.

Apart from these chemical or physico-chemical methods the organism is able to defend itself by mobilization of the wandering cells of the mesenchyme. The phagocytes are rushed to the threatened area; steps are taken to deal with the invaders by their means and by hemming them in so as to localize the trouble.

The temperature of the body also is raised to the optimum level for the altered circumstances. Such is the picture by which we arecon fronted if, as Andrewes does, we look upon fever, and inflammation also, as part of a well-devised protective scheme.

As to the part which infective diseases have played in the evolution of the human race it is difficult to bring forward any definite evidence, but still more difficult to doubt that that influence has been very great. Epidemics and pandemics have decimated, and more than decimated, large populations, as witness the Black Death in England, and, in a lesser degree, the pandemic of influenza in 1918. Such outbreaks destroy the strong as well as the weak, but less highly infectious maladies do much to weed out the feebler members of the community.

To turn to the other side of the picture it appears to be certain that populations tend to acquire a considerable degree of protection against those infective diseases with the infective agents of which they are continually in contact. The fatal results of the introduction of an infectious disease, such as measles, into a community

not previously exposed to it, bear witness to such relative, acquired immunity.

Two explanations of this suggest themselves. On the one hand there can be no doubt that repeated exposure to an infection, even though no attack of the corresponding disease results, does tend to confer a degree of acquired immunity; on the other hand it is difficult to doubt that, as Archdall Reid[1] so strongly maintained, the more susceptible members of a community tend to be eliminated by natural selection, with the result that the surviving population consists mainly of less vulnerable individuals. Naturally this applies only to the maladies which are always with us; a community enjoys no such relative immunity in face of a disease to which it has never previously been exposed.

The other side of the picture need not be discussed here, but should be alluded to. It must not be supposed that the evolutionary processes are concerned for the welfare of the higher animals alone. The bacteria and protozoa which have acquired parasitic habits have their own careers to work out; to ensure their own survival their methods of attack have doubtless been improved, to counter improved methods of defence. We must picture a struggle of conflicting interests, carried on through the ages, perhaps since the *dawn of life* upon this earth.

But by no means all maladies are due to infective agents, and in some the internal factors play by far the more conspicuous parts. The subject of an unfavourable

[1] Loc. cit

mutation may get along well enough until he be subjected to some exceptional test; but an external agent, such as an injury, of a degree harmless to an ordinary individual, may have serious consequences for him.

Unfavourable mutations of minor kinds may cause disfigurement or may inconvenience their subjects in a variety of ways, but may nevertheless recur in successive generations of a family. The conditions of civilized life tend to favour the survival of such defects; a brain worker may be little handicapped by a structural deformity of a minor kind. More serious departures from the normal may greatly diminish the chance of the sufferer's survival into adult life, and tend to die out. Others again, such as the more extreme kinds of cardiac malformations, are incompatible with survival.

Whilst a necessary factor in the improvement of the race through natural selection is the transmission by inheritance of such favourable mutations as may occur, there is abundant evidence of the hereditary transmission of such unfavourable mutations as those which entail unusual liability to disease.

IV

INHERITANCE OF MORBID LIABILITIES

Patrius hic illi, nam plerumque morbi quoque, per successiones quasdam, ut alia traduntur.—PLINY THE YOUNGER *c.* A.D. 96.

IT is obvious that the importance of heredity, in connexion with the inborn factors in disease, can hardly be exaggerated, nor can it be doubted that, apart from

direct infection of one member by another, or very special conditions of environment, a malady which occurs in several generations of a family with more than average frequency, does so in virtue of some inborn peculiarity of the stock.

Some of the chief difficulties which, until recent times, surrounded the study of inheritance have now been overcome, thanks to the work of Francis Galton and Gregor Mendel, and those who have carried on so assiduously the researches which they initiated.

Such problems as that of atavism and the skipping of generations, and the 'knight's move' inheritance of haemophilia and colour blindness, have lost most of their obscurity, and no longer present any great difficulty of interpretation.

It is not possible, in such an essay as this, to attempt to give any general account of the modern views on heredity, and it will be necessary, whilst speaking of their bearing upon the particular problems here discussed, to assume that the reader has at least some acquaintance with the Mendelian theory and the views of Galton.

It must be recognized, at the outset, that a disease or anomaly which is present at birth is not necessarily inborn. There are some diseases which may be acquired *in utero*, such as congenital syphilis, and some congenital deformities are the results of intra-uterine amputations or minor injuries. Obviously all such may be excluded from this inquiry.

The once widespread tradition of the very hereditary nature of tuberculosis, dates from the days before the infective origin of that disease was recognized, and when it was a common occurrence for brothers and sisters to succumb, one after another, to tuberculosis caught by one from another. The adoption of precautions against infection, such as destruction of sputum, improved ventilation, instead of rigid exclusion of fresh air, and the encouragement of outdoor life, have greatly diminished the frequency of such occurrences, and have diminished the importance of the part assigned to heredity in connexion with tuberculous affections.

On the other hand, the investigations of Karl Pearson,[1] Stocks,[2] and Govearts,[3] who employed statistical methods, and dealt with thousands of cases, revealed a somewhat higher incidence of tuberculosis in members of families in which the disease has occurred in previous generations than in those in which no such family history is forthcoming.

It must be borne in mind that the occurrence of the same malady, and especially of a common malady, in several members of a family, may be fortuitous, and it is essential to employ the method of control when estimating the value of evidence of inherited liability which such occurrences supply. We need to know not

[1] Drapers' Company Research Memoirs: *Studies in Natural Deterioration*, No. II, 1905.

[2] *Ann. Eugenics*, 1927, ii. 41; and 1928, ii. 84.

[3] *Eugenics Rev.*, 1926–7, xvii. 12.

only the proportion of subjects of the disease in whose families it has previously occurred, but also the proportion of unaffected individuals with such family histories, and the frequency of such histories in members of the community at large.

It is equally important that the influence of heredity shall not be under-estimated, as it well may be, seeing that the inheritance of a particular malady may be masked, and a Mendelian recessive quality may remain latent through several generations—the atavism of the older physicians. When such intervals occur the history of previous occurrence of the malady may only be elicited by diligent inquiry, if at all, for few of us are able to give any account of the ailments of our great-grandparents.

It should be noted, too, that experience shows that when tabulating recorded cases of a malady, the absence from the records of any mention of its occurrences in past generations, or of consanguinity of parents, cannot be taken as evidence of there having been none such.

Some peculiarity of environment is among possible causes of the family occurrence of maladies, but is little likely to lead to error. A deleterious trade carried on by successive generations, such as steel grinding, or contamination of the water-supply with lead, are cases in point. In the case of such diseases as goitre, endemic in particular regions, the members of the community and not of particular families are likely to be affected.

Mendelian studies throw very valuable light upon morbid predispositions, and numbers of human anoma-

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As William Bateson[1] was the first to point out, such a mating is far more likely to occur when a member of an albinotic family marries a cousin, also a member of that family, than when he or she marries into a different family, especially if the recessive characteristic be a rare one. The rarer the anomaly the higher should be the proportion of its subjects whose parents are consanguineous.

Hence it comes about that albinism, which is a rare anomaly, and has been shown to be recessive, is met with, with quite unusual frequency, in the children of consanguineous marriages. Whereas marriages of first cousins number from one to eight per cent. of all marriages in this country, the percentage of first-cousin marriages amongst parents of albinos is about forty per cent.

In estimating such percentages a sibship containing several albino brothers and sisters should be taken as the unit, not the individual albino. The number of marriages which result in albino offspring, and not the number of albinos whose parents are consanguineous is in question.

It should be noted that the marriage of cousins as such does not favour the occurrence of such anomalies, but the union of cousins both of whom are members of the family in which the anomaly runs, and both of whom contribute recessive gametes.

It is obvious that we are justified in arguing that an

[1] *Report of the Evolution Committee of the Royal Society*, 1902, No 1, p 133, note.

lies are mutations which are either Mendelian dominants or recessives. But, since for obvious reasons the relative numbers of normal and abnormal offspring in the small human families supply little information as compared with the results of experimental breeding of prolific animals, it is mainly by the application to man of the results obtained by such experimental breeding that progress has been made.

An only child may be merely the firstborn of a family, and miscarriages would need to be taken into account in reckoning human families, and at the best the figures dealt with would be incomparably smaller than those relating to mice or rabbits, and still more to such an insect as drosophila.

Albinism, a mutation occurring alike in man and lower animals, is clearly shown by experimental breeding to be a Mendelian recessive mutation, such as can only appear when both parents, although they may themselves be normally pigmented, contribute recessive gametes. If both parents be albinos all their offspring will be albinos. So long as one parent is a *true* dominant, normally pigmented, and contributes *only* dominant gametes, none of the children will be albinos; but, on the other hand, one parent or both parents may appear to be normal and yet produce both dominant and recessive gametes. Albinos may appear amongst the children of such parents, but several albino-free generations may elapse before a mating again occurs between parents who both produce recessive gametes.

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If we attempt to apply Bateson's law of 'presence and absence' to human abnormalities difficulties are apt to be encountered. Whereas some recessive anomalies appear to be due to absence of some factor, a ferment in some cases, and excess of digits is obviously dominant, as Bateson's law requires, brachydactyly, with deficient number of phalanges, also behaves as a dominant. It is probable that in some at least of the apparently paradoxical instances more than one factor is concerned.

In recent years a considerable amount of information bearing upon the inheritance of human anomalies and liabilities to disease has been accumulated. In a recent work Ruggles Gates[1] has brought together and discussed the material already available, and supplies a copious bibliography of the subject. To this and other books by British and Continental writers, the reader is referred for further information, which is outside the scope of this essay. O. Naegeli's[2] suggestive monograph may be mentioned specially.

To some examples of morbid heredity, which are of chief importance in illustration of questions here dealt with, it will be necessary to refer in later chapters.

In Francis Galton's fascinating book, entitled *Enquiries into Human Faculty*, there is a chapter upon the histories of twins, in which he remarks that 'the steady and pitiless march of the hidden weaknesses of our

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constitutions, through illness to death, is painfully revealed by these histories of twins'.

The subject is closely allied to that of heredity, if not actually a part thereof.

No other two human beings are so much alike as are twins developed from a single ovum. Their likenesses of outward form are proverbial, and have supplied the plots of tales and dramas. That such twins also resemble each other in mental attributes, disposition, and tastes, is equally well recognized; and it may safely be inferred that the resemblances extend still deeper, to their tissue structure, and to the metabolic processes which constitute their chemical life. It has been shown that there are close resemblances of such essentially individual features as finger prints, sole prints, and blood groups.

Here obviously is a most promising field for inquiry into the inborn factors in disease, for, as His says[1], when there occur in uniovular twins, at like ages and with similar courses, diseases, such as pneumonia or rheumatism, which we are accustomed to regard as maladies due to exposure or occupation, we recognize the powerful influence of constitution upon them.

A large amount of information upon this subject is available, but much of it has not the accuracy demanded, if the evidence is to be regarded as conclusive. What is needed is a collective investigation based upon information supplied by medical men who have been in contact with the twins from birth upwards,

[1] *Ueber die natürliche Ungleichheit der Menschen*, 1928, p. 18.

supplemented by other information from lying-in wards and hospital notes. In Galton's chapter, based upon answers to a questionnaire, the information was for the most part supplied by the twins or their parents, and little of it by their medical attendants.

On the other hand, notable contributions from the medical side have been made by George Murray[1] and E. A. Cockayne[2] in this country, and by Siemens[3] and others in Germany. Julius Bauer,[4] in his book on Constitution, cites a number of examples of disease in twins in his discussion of constitutional factors in particular diseases.

Obviously it is essential that in any collective investigation of the subject the inquiries must discriminate between true, uniovular twins and those developed from separate ova, but the latter will be of use as controls. In so discriminating it is easy enough to discard all cases in which the twins are of different sexes, as being obviously binovular, but it is far from easy to discriminate between mono- and hetero-zygotic twins of the same sex, and the latter, according to Newman, constitute half of the total number of twins of one sex. Evidence of a single placenta, of one chorionic and two amniotic membranes is essential when dealing with crucial cases. Apart from such cases the error resulting from accept-

[1] *Lancet*, 1925, i. 529
[2] *Brit. J. Child. Dis.*, 1911, viii. 487.
[3] *Zwillingspathologie*. 1924.
[4] *Die konstitutionelle Disposition zu inneren Krankheiten*, 2nd ed. 1921.

ance as presumably uniovular of twins of the same sex, and whose likeness to each other is conspicuously greater than that of ordinary brothers or sisters, will not be a large one. As examples of the crucial questions referred to, in which such evidence does not suffice, may be quoted that of differences of blood groups in twins, and the occurrence of Mongolian idiocy in one of the pair.

The number of records which fulfil the strict requirements are very small, but the following may be quoted as such. Cockayne and Sheldon[1] described the cases of male twins both of whom exhibited signs of congenital pyloric stenosis in the earliest months of life. In both cases the diagnosis was confirmed at an operation. It was testified by the midwife who attended the mother that there had been one placenta, one chorion, and two amniotic sacs.

Other cases of pyloric stenosis in identical twins have been recorded.

There is much evidence which hardly admits of question, of the tendency of the so-called identical twins to develop along similar lines, even when their surroundings and upbringing are different. In Galton's[2] words, 'they continue their lives, keeping time like two watches, hardly to be thrown out of accord, except by some physical jar'.

There is also an impressive mass of evidence that

[1] *Proc. Roy. Soc. Med.*, 1928, xxi 1260
[2] *Inquiries into Human Faculty*, 1883, p 235.

true twins are wont to suffer from the same illnesses almost simultaneously, even though living far apart and in different circumstances.

One is tempted to be sceptical as to such records, but it is hard to doubt the testimony of Trousseau[1] as regards the often quoted case of twin brothers who were attacked simultaneously with 'rheumatic ophthalmia', in Paris and Vienna respectively, and who both suffered from asthma. In this, as in other recorded cases the one twin foretold the other's attack. Trousseau adds, that however singular this story may appear, the fact is none the less exact; it was not told him by others, but he has seen it himself; and has seen other similar cases in his practice.

There are not a few instances of similar troubles developed by twins well on in life, and in some of these the maladies observed have not been such as might be expected to be hereditary.

Among such are Hodgkin's disease, lymphatic leukaemia, Hirschsprung's disease, and Hanot's cirrhosis of the liver, papilloma of the larynx, and even empyema and pneumonia. Amongst the records scattered through Bauer's book are some of Fröhlich's syndrome, calcaruria, renal tuberculosis, and various nervous disorders, including myatonia congenita and spastic paraplegia. Such cases are not numerous enough to serve as bases of generalization, but they emphasize the desirability of systematic research upon rigid lines.

[1] *Clinique Médicale*, 1861, tome i, p 523.

Of exceptional interest and importance are the examples of diabetes in twins collected by W. Stanley Curtis[1] of Boston. *They relate to thirteen pairs of twins*, several of which were under observation in the Joslin clinic, and it is necessary in this connexion to take into account not only the several kinds of twinship but also the several kinds of glycosuria, some of which appear to be manifestations of definitely inborn peculiarities, such as the glycosuria without hyperglycaemia, the so-called diabetes innocens.

Of Curtis's thirteen pairs of twins one pair was of different sexes, and two other pairs are described as not homologous, although of the same sex. The remainder are classed as identical twins. It is of interest to note that the ages at the period of onset of the diabetes varied within such wide limits as three to sixty years. Twin brothers of fifty-nine, died of diabetes within two months of each other, and brothers of sixty within a few weeks. Yet a third pair of brothers succumbed to the disease within four months of each other, at the age of twenty-seven.

Such cases recall Galton's simile of the watches which run down together.

In other cases there were long intervals between the onsets of the malady; and as evidence of the difficulties which beset such inquiries, Curtis tells that the mother of the twins of different sexes declared that they always had the same diseases.

[1] *Jour. Amer. Med. Ass*, 1929, xcii. 952.

It must be acknowledged that there is something uncanny about the diseases of twins.

Each of the subjects so far discussed has important bearings upon questions of constitution, of human individuality, and upon what Langdon Brown[1] has called predestination to disease. The attempt may now be made to apply the knowledge gained in recent years of the chemical constitution and activities of the human body to the elucidation of the processes at work in rendering it unduly liable to, or unduly immune from, diseases of various kinds.

[1] *Brit. Med. Jour.*, 1930, i. 525.

PART II

THE SEVERAL KINDS OF PREDISPOSITION

V

STRUCTURE AND FORM IN RELATION TO DISEASE

Each patient has a pathological, as well as a mental and social individuality.—THOMAS LAYCOCK, 1862.

THE relationship of structure to disease has to be considered under two main aspects. In the first place peculiarities of form or feature may serve as labels indicative of liability to particular maladies, although no obvious part in the causation of those maladies can be assigned to them. On the other hand, some deviations from the average build and structure of the species render their possessors liable to pathological accidents of various kinds.

It has long been recognized that, as regards their liability to disease, people fall into different classes, and that such liabilities may be associated with differences of structure and feature; so that the several 'temperaments', to use the term in its older sense, may often be recognized by mere inspection.

Various factors doubtless contribute to the production of those groups of individuals who resemble each other, not only in outward form, but also in physiological

and mental processes. Amongst these the accumulated effects of inheritance play important parts.

In a race such as ours, which results from the fusion of a number of strains, and especially of Kelt, Anglo-Saxon, and Northman, racial peculiarities must contribute largely; and just as racial characteristics extend to the forms and agglutinations of the red corpuscles of the blood, so also there is a considerable mass of evidence pointing to racial liabilities to, and immunity from particular diseases.

In recent years the study of such individual differences of structure, and of the morbid proclivities associated with them, has been approached along modern scientific lines, and by the employment of anthropometric methods. Such anthropometric studies, together with others involving different methods, but similar in their aims, are being pursued in the 'Constitutional Clinics' which have been established in several centres. George Draper,[1] who presides over such a clinic in New York, has already published a volume dealing with what he describes as the 'anatomical panel', and which embodies the results of large numbers of measurements, and deals with statistics relating to many individual men and women as regards their stature, girth, weight, and any physical peculiarities of feature or limb which they exhibit. This investigation is only a part of that contemplated in Draper's scheme, which embraces also physiological, psychological, and immunological panels.

[1] *Human Constitution*, 1924.

To turn to the second division of the subject under discussion, namely the part played by anatomical anomalies in predisposing their subjects to disease, it is surprising, at first sight, to find how small that part is. Important as is the part which disease plays as an instrument of natural selection, it is rather those who are functionally than physically unfit who are weeded out by its means.

Yet in extreme cases congenital malformations may be incompatible with survival; or as is the case with certain cardiac defects, may seriously curtail life. Malformations of less degree may place their subjects at serious disadvantage, by disfiguring them, by hindering them in earning a living, or by impairing their powers of self defence.

It is hardly necessary to point out that malformations differ widely in kind. Some are due to failure to complete some structure, and to this class of malformations by defect belong hare-lip, cleft-palate, and spina bifida. Others are malformations by excess, such as extra digits, and others again, such as branchial clefts, present persistent vestigial remnants. Many malformations are obviously hereditable, either as dominant or recessive characteristics, and it would seem that in some families what is inherited is a tendency to structural variations, rather than any individual anomaly.

On the other hand, it cannot be supposed that the evolution of the human frame has reached its limits, nor that all variations of form are necessarily harmful;

of may be met with from time to time. For example, an almost complete absence of the muscles of the abdominal[1] wall occurs in association with enormous dilatation of the ureters, and of the bladder which is usually attached to the umbilicus. The condition is usually fatal in infancy, but some subjects have survived to adult life. It is not certain which is the primary event, but examination of subjects of the anomalies leaves little room for doubt that the abdominal distension due to the huge bladder leads to atrophy of the affected muscles.

However, such combinations and happenings rank rather as clinical curiosities than as examples of structural predisposition to morbid states; and as such they contribute but little to the elucidation of the problems of predisposition. Far more germane thereto, but still of the nature of curiosities, are the cases in which a malformed part serves as a seat of election of an infective process. Thus it is a recognized fact that malformed cardiac valves are favourite seats of malignant endocarditis, and specimens are to be seen in museums in which the abnormal curtains alone have been attacked. Yet such cases also contribute only a very minute fraction to the total of cases of such endocarditis.

Vestigial remnants, also, may be sources of danger to those who possess them. Thus a Meckel's diverticulum may not only give rise to strangulation of the intestine, or to intussusception, but it also appears to

[1] Garrod, A. E. and Davies, H.W., *Med.-Chir. Trans.*, 1905, lxxxviii. 363.

although in the course of ages the body has become so well adapted to its surroundings that, in its ordinary environment, any conspicuous change is more likely to be harmful than beneficial.

When an important organ is malformed its function may be impaired. The subjects of congenital cystic disease of the kidneys may show few symptoms for years, but eventually they usually succumb to progressive renal disease. That this anomaly is inborn is shown by its occurrence in successive generations of a family; as in families described by H. W. B. Cairns[1] and C. J. Fuller,[2] in one of which it was traced through four generations. There is still much to be learned as to the initial stages of the anomaly, and some hesitation is permissible in deciding whether to place it under the heading of malformations or that of tissue-defects. The cyanosis and clubbing of the digits in cases of cardiac malformation may be cited as other examples of secondary effects of structural anomalies.

In a case seen by the writer, a young woman died suddenly in an uraemic convulsion, due to pressure of an enlarging uterus upon a single small kidney, situated in the hollow of the sacrum; again abnormal mesenteries of the caecum or colon may lead to intussusception or volvulus, even in later life.

Occasionally a definite clinical picture is presented by a group of congenital anomalies, and examples there-

[1] *Quart. Jour. Med.*, 1924–5, xviii. 359.
[2] Ibid., 1928–9, xxii. 567.

of may be met with from time to time. For example, an almost complete absence of the muscles of the abdominal[1] wall occurs in association with enormous dilatation of the ureters, and of the bladder which is usually attached to the umbilicus. The condition is usually fatal in infancy, but some subjects have survived to adult life. It is not certain which is the primary event, but examination of subjects of the anomalies leaves little room for doubt that the abdominal distension due to the huge bladder leads to atrophy of the affected muscles.

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sign of a long one. Both may be regarded as variants from the average form of stomach met with in normal people, as being independent of gastric tone, and of the amount of support afforded by the abdominal wall.

Moreover, hyperchlorhydria, which has been shown by Ryle[1] and others to be commonly associated with a short stomach, and hypochlorhydria usually associated with a long one, are physiological variations from the average of gastric secretion. They are both met with in normal individuals. It is not suggested that the type of secretion is *dependent* upon the length of the stomach, but that the associated conditions are wont to coexist in individuals of particular structure and build. Furthermore, such conditions may predispose to disease of particular kinds; such as duodenal ulcer, which is apt to occur in those whose stomachs are short, and whose gastric juice is unduly rich in hydrochloric acid.

The intimate connexion between structure and function here suggested, has been alluded to in earlier chapters. The trifling deviations of form and function which are revealed by anthropometry, and by physiological tests may be looked upon as slight oscillations, such as are bound to occur, to one side or another of an imaginary normal line. Such trifling innovations may furnish clues to the gifted facial diagnostician, and wider deviations may offer much more obvious warning signals, even though the anomaly may be one of function and not of structure.

[1] *Guy's Hosp. Gaz.*, 1926, xl 546.

VI

TISSUE DEFECTS.—ABIOTROPHIES

Es angeborene embryonale Defekte gibt, bei deren Bestehen die normale Funktion schon eine Schädigung bedeute —O. ROSENBACH, 1891.

IN *the conditions next to be discussed, the congenital* defects are not of particular organs, but of tissues of particular kinds. In some instances there are present from birth, obvious changes in the affected tissues, inherited from former generations, and which have none of the characters of progressive diseases. Sometimes the only outward sign of defect of internal tissues is some warning signal, in a conspicuous situation, such as blueness of the sclerotics of the eyes. In some instances there develops upon the top of the congenital defect a progressive morbid process, and, occasionally, stationary tissue defects and progressive changes are mixed together to form a complex clinical picture. Lastly, there are maladies, inherited and obviously inborn, in which there are no obvious tissue defects at birth, nor in early *childhood, but in which there appear, at some period* in early life, signs of a progressive disease. The best examples of these last are to be found in the heredo-familial diseases of the neuro-muscular system, to which Gowers gave the name of 'abiotrophies'.

Such conditions found no place in the diathetic lists of our forefathers, although they offer some of the most striking examples of inborn tendencies to special forms of disease, or more strictly, to disease of special tissues.

Doubtless their omission was mainly due to the fact that very little was known about these maladies at the time when the idea of diatheses was to the fore, and that of some of them nothing was then known. They have no place in Hutchinson's *Pedigree of Disease*, although its author mentions that he has met, in his practice, with inherited liability of kindred tissues to exhibit inflammation of peculiar forms, at certain ages, and as effects of very insignificant causes.

Among the tissue defects which may be regarded as congenital malformations rather than as progressive maladies, those which involve the surface tissues are naturally the most obvious. They are usually hereditary in a pronounced degree. Ichthyosis, and tilosis of the palms and soles are familiar examples, but in recent years increasing attention has been given to a rare and most remarkable form of ectodermal defect. It has been described as incomplete development of the epidermis and its dependencies, amounting sometimes to its absence over circumscribed areas. The anomaly was first described by Goeckermann[1] in the year 1920, and among those who have studied it since may be mentioned Christ,[2] MacKee and Andrews,[3] and Falkoner[4] of Capetown.

One of its most striking features is a partial or com-

[1] *Arch. Dermat. and Syph.*, 1920, i. 396

[2] *Arch. f. Dermat. u. Syph.*, 1913, cxvi. 685.

[3] *Arch. Dermat. and Syph.*, 1924, x. 673.

[4] *Lancet*, 1929, ii. 656.

plete absence of teeth. The nasal bridge is usually depressed, the skin is dry, smooth and glossy; and owing to the lack of sweat glands the victims of the anomaly suffer much discomfort in hot weather. The sebaceous glands are also absent and the hairs scanty.

The defect is strongly hereditary and in some instances the dental defect has been the only visible sign in some members of an affected family.

Here we have an example of a hereditable defect limited to tissues of a particular class, namely ectodermal, which are embryologically connected.

In another group it is in the bony structures that the shortcomings are mostly observed. A noteworthy example is afforded by the hereditary form of brittleness of the bones which has been observed in large numbers of the members of successive generations of some affected families. The fragility is apparently due to a defect of the mesenchyme, leading to an imperfect formation of connective tissues, rather than to any imperfect laying down of calcium salts in the bones; for the blue colour of the sclerotics of the eyes of those members of a family in which the condition occurs, is certainly due to imperfection of the fibrous tissue of the sclerotics, which, being less opaque than it should be, allows the black pigment of the choroid to show through it. An analogous blue colour, due to the blackened cartilage showing through the skin, is seen in the hollows of the ears in cases of ochronosis.

The blue sclerotics serve as warning signals of the

presence of the anomaly of the bones, and also bear eloquent witness to the inborn and congenital nature of that anomaly.

The affected members of such a family suffer repeated fractures of bones from what appear to be wholly inadequate causes; their skeletons are unable to bear the wear and tear of daily life.

The fractures occur at any period of life, from early childhood onwards; and as life goes on the majority of the victims develop the changes in the aural structures known as otosclerosis, manifested by progressive deafness. There can be no question of the association, for otosclerosis has been met with in many subjects and in members of various affected families.

Here then we have a very instructive combination of three factors in a morbid picture. First the visible warning signal the blueness of the sclerotics, secondly the inability to resist slight traumata, manifested in the repeated fractures of bones as the results of slight injuries, and thirdly the progressive deterioration of the structures of the ears, the otosclerosis. And with it all we have one of the most striking of known examples of hereditary transmission of a defect met with in the whole field of pathology.

In recent years the use of the X-rays has brought to light a still rarer form of brittleness of bones. In cases of this condition the shadows cast by the bones are uniformly dark, as if they were solid throughout, which they actually are in advanced cases. Here the brittle-

plete absence of teeth. The nasal bridge is usually depressed, the skin is dry, smooth and glossy; and owing to the lack of sweat glands the victims of the anomaly suffer much discomfort in hot weather. The sebaceous glands are also absent and the hairs scanty.

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point has been made, no evidence of family occurrence has been forthcoming. This fact presents a serious obstacle to the inclusion of the disease in the group under discussion. Against it may be set the remarkable fact that in no less than 70 per cent. of all recorded cases there have been *congenital* deformities of the great toes, and in some cases, of the thumbs also. The nature of the deformities is not so constant as their seats, but in most instances the affected digits are *shortened*, either by suppression of a phalanx or by fusion of phalanges.

In one instance a father who had such digital deformities, but *no* myositis, begat a son with identical deformities who developed *myositis* ossificans in early childhood.

It is difficult to imagine what is the connecting link between the malformations and the malady, unless the latter has an inborn basis, and as has been mentioned in connexion with ectodermal defect, the widening of the extent of a tissue anomaly in successive generations of a family is not an uncommon phenomenon.

We are probably justified in including amongst tissue defects certain familial and hereditary diseases which are characterized by anomalies of the red blood corpuscles and leucocytes, and especially that known as acholuric jaundice, or, preferably, as congenital haemolytic jaundice. It was Chauffard who first pointed out that the red corpuscles of the subjects of that malady undergo haemolysis in saline solutions not sufficiently dilute to haemolyse those of normal blood, or as it is

ness is presumably due to loss of tubular structure, and also to diminished elasticity of the affected bones. It would seem that such osteosclerosis is progressive, for various degrees of obliteration of the marrow cavities have been observed; but it is so rare, and has been so seldom met with, that it would be premature to base any sweeping conclusions upon the scanty knowledge which we have of it. It is almost certainly a Mendelian recessive, and like other such, has been met with unduly often in children of first cousins. It is a matter of no small interest that in some advanced cases of such osteosclerosis, there has been enlargement of the spleen and lymphatic glands, as if to compensate for the destruction of the bone-marrow.

That remarkable and bizarre malady known as, myositis ossificans progressiva is of even greater interest in connexion with our subject. In it also the mesenchyme is the seat of the defect, and Julius Bauer suggests that in those who suffer from it the cells of the mesenchyme retain the power which they normally lose, of forming bony tissue [1], for it is in the connective tissue around the affected muscles that the osseous deposits are formed. It is noteworthy that a similar bone-formation is occasionally seen as a localized result of a severe local injury.

It must be acknowledged that the evidence of inheritance of myositis ossificans is, up to now, very scanty, and in the majority of cases in which inquiry upon this

[1] *Die konstitutionelle Disposition zu inneren Krankheiten*, 2nd ed., 1921, p. 330

point has been made, no evidence of family occurrence has been forthcoming. This fact presents a serious obstacle to the inclusion of the disease in the group under discussion. Against it may be set the remarkable fact that in no less than 70 per cent. of all recorded cases there have been congenital deformities of the great toes, and in some cases, of the thumbs also. The nature of the deformities is not so constant as their seats, but in most instances the affected digits are shortened, either by suppression of a phalanx or by fusion of phalanges.

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usually stated, are abnormally 'brittle'. Naegeli[1] made the further observation that the red corpuscles of a patient with haemolytic jaundice, although they appear unduly small under the microscope, actually exceed normal erythrocytes in volume. From this he concludes that they are more globular in form.

The peculiarities of the red corpuscles, their brittleness and unusual form, are obviously independent of the medium in which they are suspended, and it has not, apparently, been shown that normal red corpuscles are rendered brittle by contact with the serum of a subject of haemolytic jaundice.

Naegeli holds, moreover, that the abnormality of the corpuscles is the primary feature of the malady which only manifests itself by visible signs under the influence of external agencies such as infections or poisons. The enlargement of the spleen and the haemolysis he regards as secondary phenomena, for he finds that the abnormal form of the erythrocytes persists, and their brittleness is only diminished slightly after removal of the spleen. The remarkable improvement which follows splenectomy, and which amounts, in some cases, to practical recovery, he attributes to the withdrawal of the haemolytic action of the spleen. Lastly, Naegeli classes the condition as a mutation of the Mendelian dominant class.

Hawkins and Dudgeon[2] made the interesting sugges-

[1] *Allgemeine Konstitutionslehre*, 1927

[2] *Quarterly Journal of Medicine*, 1908–9, ii, 165

tion that the brittleness of the red corpuscles may be due to a deficient stability of the haemoglobin contained in them; interesting because if verified it would bring congenital haemolytic jaundice into line with morbid states obviously due to chemical abnormalities.

Yet another borderland malady, on the frontier of structural and chemical anomalies, is that which is called, after its discoverer, Gaucher's disease. Here, as in the instance of dystrophia myotonica, to be referred to later, we meet with a history of greater and greater extension of a clinical and pathological picture, each step forward throwing fresh light upon the pathogeny of the trouble. The story dates back to the year 1882, in which Gaucher[1] described a condition of primary epithelioma of the spleen, a kind of splenomegaly met with by him in a child, and characterized by the presence in the splenic tissue of many large hyaline cells which stained only feebly. Since then a number of such cases have been observed, in all of which there has been the same microscopic picture, which is quite unlike any observed in other varieties of splenic disease. As the fresh cases were investigated it soon became evident that this was no variety of malignant tumour, and that the morbid changes were by no means limited to the spleen.

As the disease progresses the liver undergoes great enlargement also, and the haemopoietic tissues generally, including the bone marrow, become involved, and not merely in a secondary manner; for the characteristic

[1] *De l'Épithélioma Primitif de la Rate. Thèse de Paris*, 1882

inborn anomaly of metabolism, by which the metabolic path is perverted rather than arrested at an intermediate stage. He compares the deposition of the Gaucher substance with the similar laying down of abnormal chemical material, such as fat out of its proper place, in the reticulo-epithelial tissues of sufferers from diabetes.

To turn now to the abiotrophies of Gowers,[1] in which there is in many instances atrophy of muscular fibres or nerve cells and fibres, which Gowers described as a wasting away of tissues, as of plants without soil, and its replacement by fibrous tissue, 'tissue weed' as he called it. But this designation as tissue weed is not altogether a happy one, for the fibrous tissue may be more aptly compared to the rubble with which a breach in a fortress wall has been repaired. It represents an attempt to mend; the best that Nature can do to make good the loss.

Some of the neuro-muscular abiotrophies, and especially that peculiar kind known as pseudo-hypertrophic muscular dystrophy, are sex-linked Mendelian recessives, transmitted almost always by normal females to their male offspring. Others behave as simple recessives and some as dominant characters.

The onset of such a malady, or rather its manifestation by obvious signs, is wont to occur at about the same age in the several affected members of a sibship (a set of brothers and sisters), but there is a tendency for the age of onset to anticipate from generation to generation. As Mott suggested, but in another connexion,

[1] *Lancet*, 1902, i. 1003.

diseases which behave in this manner tend to eliminate themselves from the stock in which they occur, by a virtuous circle so to speak; whereas sex-linked recessive characters tend to secure their own survival, seeing that the healthy members of the family transmit the defect.

Up to now little is known of the state of the affected tissues in the stage before the disease becomes apparent. The rarity of most of these tissue defects renders such inquiries difficult, but systematic examination of the children of the affected families might meet with some reward. Abnormalities of individual muscles in association with the tissue defect have been described as met with in some cases, and in others, areas of change have been found in muscles not yet obviously involved. Of less importance, save as affording evidence of structural instability, are malformations of various kinds which have been met with in such cases. Such malformations of minor degree are common enough, and comparative statistics of their occurrence in myopathic and other individuals are necessary if we are to judge the value of such evidence.

The abiotrophies of the neuro-muscular system differ conspicuously amongst themselves in their clinical features, which is not surprising seeing that the clinical pictures of nervous diseases are shaped largely by the situations of the lesions. In some of them muscular atrophy is the conspicuous manifestation, in others muscular spasm, and in others again atrophy and spasm in association. Some again, such as Friedreich's ataxia,

are manifested by inco-ordination and tremor. It is noteworthy, moreover, that the various types of such affections do not appear to breed true, for different members of the group have been met with in different members of the same family.

That a neuro-muscular defect may be merely the conspicuous sign of a far wider morbid picture, is well illustrated by the growth of our knowledge of that one of them which goes by the name of dystrophia myotonica. The story is well told in a paper by Adie and Greenfield,[1] published in 1923.

The first step was the recognition, in a special group of cases of myotonia (the condition of which Thomsen's disease is the best-known form), of the association with the muscular spasm, of muscular atrophy of somewhat unusual distribution, facial, brachial, cervical, and in some cases, peroneal. This association is named, after those who first described it, the Batten, Steinert, Curschmann syndrome. The second step was the observation that, with the above syndrome, cataract is wont to be associated, either in the patients themselves, or in members of previous generations of their families. Later still, it became evident that the dystrophy, myotonia and cataract are one and all manifestations of a still more comprehensive hereditary and familial disease, amongst the other signs of which are changes in the thyroid gland, testicular atrophy, baldness, increased secretion of sweat and tears, with cyanosis and coldness of the

[1] *Brain*, 1923, xlvi. 73.

extremities. This somewhat confused clinical picture has suggested to some observers that behind it is a widespread defect of endocrine glands—that it is a pluriglandular syndrome, in fact.

It is noteworthy that whereas in the cases hitherto reported the dystrophy and muscular spasm have been met only in collaterals belonging to a single generation of a family, and in them has seldom developed under the age of twenty-five years, the cataract has been traced back through four or five generations of that same family.

No one who has watched the course of the diseases here grouped together under the name of tissue defects, can doubt that inborn factors play very large parts in their causation. The development of a characteristic syndrome in member after member of a family, and often in members of successive generations; its appearance at about the same period of life in the members of a generation, and its tendency, in most instances, to anticipate from generation to generation, suffice in themselves to prove the importance of the constitutional element. Further evidence is afforded by the warning signals sometimes shown, which may attract attention even during the latent period of the malady. On the other hand, it is difficult to conceive of the steady progress of such maladies unaided by any external influences, even if we are driven to invoke as such the innumerable minimal insults which constitute the wear and tear of daily life. It may well be true as Rendu

wrote, in an article on Gout, 'C'est d'ailleurs une loi générale que le traumatisme éveille souvent la prédisposition diathésique'.

The subject of a constitutional defect who suffers from obvious lesions when exposed to some particular external influence may have remained quite unaware of his liability until he was exposed to such influence; a subject of Raynaud's disease may exhibit no symptoms until he removes from a hot climate to a cold one. Whether it would be possible by any special care to avert a neuro-muscular abiotrophy remains unknown.

Nor can any answer yet be given to the question whether, in cases of congenital and hereditary tissue defects, the structure or make-up of the affected tissues is at fault, or whether their resistance is impaired by some unusual metabolic product present in them. The only positive indications of abnormality are afforded by Naegeli's observations upon the red blood corpuscles in congenital haemolytic jaundice, and by some abnormalities of muscle cells in Thomsen's disease and in some dystrophies, but in the blue sclerotics associated with fragility of bones there is visible evidence of tissue deficiency present from birth.

That chemical substances exercise selective action upon particular tissue is not open to doubt, as witness the staining of cartilages by homogentisic acid and of bones by porphyrin, and the deposition of sodium urate in the cartilages of the gouty; also the symptoms of not

[1] *Dict. Encyclop des Sci. Méd*, 1884, x 73

a few forms of acute poisoning bear witness to selective actions. However, there is as yet no evidence of the presence in the blood or tissues of any such selective agent in any of the conditions which have been considered in this chapter, with the exception of Gaucher's disease which differs in several respects from other members of the group spoken of as abiotrophies.

If the defect be in the make-up of the tissues it is probably due to errors of chemical structure, rather than to mere morphological anomaly.

Whatever their nature, the tissue defects, or some of them at least, teach us the important lesson that maladies which only manifest their presence some years after birth, or even during adult life, may have their origins in some peculiarities of the germ plasm which may be completely latent in the earlier years of life.

VII

ERRORS OF METABOLISM

Diathetic diseases are apparently generated and sustained by an intrinsic blood-poison, resulting from some perversion of the nutritive processes of the individual.—W. H. WALSHE, 1855.

IN the discussion of the parts played by derangements of function as inborn factors in disease, it will be convenient to consider the subject under three headings. In the first of the three sections there will call for discussion the parts played by errors of metabolism which can be detected and studied by the methods employed

in the chemical laboratory, and this study seems to bring us into closer touch than does any other with those underlying causes which determine the liabilities of some individuals and the immunities of others.

In the second section there will be considered the evidence for and against the existence of inborn predispositions to, and defences against, particular infective maladies—subjects of which our knowledge is far less precise as yet. It is well recognized that chemical agents play very important parts as means of defence of the patients, and as weapons in the armament of the invading organisms; but as yet we have no clear knowledge of such agents as chemical compounds, and can only recognize their presence by their physiological actions, and usually by single properties which they possess, just as if we knew nothing of strychnine save its power of causing convulsions, nor of morphine save as an inducer of sleep.

Yet we may confidently expect that as time goes on, antitoxins and their congeners will be isolated as pure substances, and that their constitution will be known, just as the hormones adrenalin and thyroxin have already been isolated and synthesized.

A third chapter will be devoted to a brief survey of the bearing upon our thesis of the so-called idiosyncrasies; in virtue of which substances contained in particular foods, certain drugs and exhalations of particular animals or plants produce in some people effects wholly out of proportion to any which they bring about in

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in the chemical laboratory, and this study seems to bring us into closer touch than does any other with those underlying causes which determine the liabilities of some individuals and the immunities of others.

In the second section there will be considered the evidence for and against the existence of inborn predispositions to, and defences against, particular infective maladies—subjects of which our knowledge is far less precise as yet. It is well recognized that chemical agents play very important parts as means of defence of the patients, and as weapons in the armament of the invading organisms; but as yet we have no clear knowledge of such agents as chemical compounds, and can only recognize their presence by their physiological actions, and usually by single properties which they possess, just as if we knew nothing of strychnine save its power of causing convulsions, nor of morphine save as an inducer of sleep.

Yet we may confidently expect that as time goes on, antitoxins and their congeners will be isolated as pure substances, and that their constitution will be known, just as the hormones adrenalin and thyroxin have already been isolated and synthesized.

A third chapter will be devoted to a brief survey of the bearing upon our thesis of the so-called idiosyncrasies; in virtue of which substances contained in particular foods, certain drugs and exhalations of particular animals or plants produce in some people effects wholly out of proportion to any which they bring about in

average individuals. Such effects vary from a slight and temporary discomfort to morbid syndromes which amount to severe or even fatal illnesses. Of these latter asthma offers a most striking example.

Whatever may have been at the back of the mind of Germain Sée[1] when he wrote of predisposition as 'cet état intermédiaire qui n'est pas encore la maladie—mais qui n'est déjà plus la santé parfaite', or of Jonathan Hutchinson,[2] when he spoke of a diathesis as 'any condition of prolonged peculiarity of health, giving proclivity to definite forms of disease' their definitions are applicable in a remarkable degree to the conditions which now call for consideration.

It has been seen how, in any theory of the nature of tissue defects, there are gaps which cannot be bridged over in the present state of our knowledge. The conditions now to be considered give more encouragement to students of constitutional factors, for in some at least of them it is possible to fathom the means by which predisposition to a disease is brought about.[3]

They show how a product of metabolism, when present in the tissues from birth throughout life, may work mischief in the course of years. Such a product, although not directly harmful, may nevertheless place an individual at a disadvantage, by rendering him liable to

[1] *Leçons de Pathologie expérimentale. Généralités*, p. xiii. 1867.

[2] *The Pedigree of Disease*, 1884, p 71

[3] Garrod, A. E., *Inborn Errors of Metabolism*, 2nd ed, 1923 (gives many references to literature of the subject).

suffer, in some obvious way, when exposed to such external influences as infections, exposure to bright light, traumata, slight or severe, or even to the wear and tear of daily life.

The chemical agent concerned may be a product of normal metabolism formed in undue amount, or an intermediate product which escapes the further changes which it normally undergoes, or possibly an abnormal product formed owing to deflexion of a metabolic process from its normal path.

The individual who carries such a substance in his tissues can hardly be said to suffer from any disease, and it may well be that his anomaly is harmless or even helpful to him. On the other hand, he is *not in perfect* health if he is rendered by it unable to adjust himself to his environment, that is to say to the influences to which a man is habitually exposed.

Seeing that no two individuals of a species, *nor even* uniovular twins, are exactly alike in structure and outward form, seeing also that the standard of chemical structure and chemical process is *no rigid one*, but represents an average, it can hardly be that *in their* chemistry, as in their structure, any two individuals are exactly alike. There is indeed much evidence of chemical individuality, as well as of chemical specificity.

In section ii it was pointed out also, that the structure of the molecules of proteins is capable of colossal numbers of different groupings and proportional compositions, but seeing that deviations from the *metabolic*

average are of necessity less obvious than variations of form, they attract comparatively little attention. It can hardly be doubted that the great majority of minor chemical variations have hitherto escaped observation.

The more pronounced chemical mutations which come under observation from time to time are clearly hereditary, and are extremely rare for the most part. The search for minor mutations revealed by no conspicuous appearance or by response to a widely used test, may be compared to the proverbial search for a needle in a haystack. Hitherto, the few recognized chemical abnormalities have attracted attention by some warning signal, comparable to the blue sclerotics of the subjects of fragilitas ossium. A systematic search for chemical mutations which show no such signs would involve elaborate metabolic studies of large numbers of specimens from many human beings, and the labour so expended would usually prove vain. Even a very limited experience of such searches served to deter the writer from pursuing further so discouraging a task.

In connexion with the known chemical anomalies the factor of inheritance plays a no less important part than with structural malformations. Most of them are recessive characters in the Mendelian sense, and this suggests that the defects are rather negative than positive. There is some tendency to sex-linkage, seeing that in the case of those defects of which a considerable number of examples have been observed, the males have been about twice as numerous as the female subjects.

It is difficult to imagine that this male preponderance, which holds good for the rare and conspicuous inborn errors of metabolism, can apply to chemical mutations in general. We can hardly suppose that the metabolism of males is far more liable to go wrong than that of females, despite its liability to do so in certain particular ways.

Although it would seem that a product of normal metabolism, even an intermediate product which should have only a momentary existence, should be little likely to be injurious to the organism in which it is formed, some at least of the chemical mutations give rise, sooner or later, to serious troubles. But such troubles are usually, if not always, provoked by some external influence. In some instances this comes about much sooner than later, as for example in haemophilia, the sex-linked recessive anomaly, due almost certainly to the lack of some enzyme concerned in the coagulation of the blood; whereas in other conditions the morbid events may only make their appearance late in life.

The subject of an inborn error of metabolism may go through life unaware of his trouble so long as he is protected from those external influences which provoke its evil manifestations.

In the days when the diatheses held the field, little was known of such chemical abnormalities, but one of them, namely cystinuria, was included by Walshe in his list of diathetic disorders, contained in a lecture delivered in 1855.[1] Wollaston, who was the pioneer in the

[1] *Med. Times and Gaz.*, 1855, xxxi. 613.

chemical investigation of calculi, described, in 1810, a previously unknown variety of urinary calculus, which consisted of a chemical compound also unknown before that date. To this he gave the name of cystic oxide, for which Berzelius substituted that of cystin. Some fifteen years later the characteristic colourless hexagonal crystals of cystin were found in urine, first by Stromeyer, and soon after independently by Prout. Not until twenty years after its discovery was the fact that cystin contains sulphur recognized. For many years urinary calculi and deposits were the only known supplies of cystin. Whence it was derived remained a secret, and to all appearance it had no place in the ordinary scheme of human metabolism.

Only at the very end of the nineteenth century was it shown that cystin might be obtained in abundance by hydrolysis of hair. This discovery, which we owe to K. A. H. Mörner, was quickly followed up, and before long cystin took its place as one of the amino-acid fractions of which the protein molecules are built up, and one of the most important of these, since it contains the bulk of the sulphur which enters into the composition of proteins.

It was Alexander Marcet, a friend and contemporary of Wollaston, who first described the occurrence of cystinuria in several members of the same family. This observation has been abundantly confirmed by subsequent observers, and in some instances the anomaly has been traced through several generations. Unlike

most other anomalies of its kind, the mode of inheritance of cystinuria suggests that it is a dominant character.

In 1888 it was shown, by Baumann and Udranszky, that cystinurics sometimes pass in their urine, and in the faeces also, the diamines cadaverine and putrescine, which can only have been derived from the argenin and lysin of proteins. This observation also has been abundantly confirmed, but it is noteworthy that these diamines, or either of them, are not to be detected in the excreta of a large proportion of cystinurics, and when found are usually present only intermittently. More recently lysin and argenin themselves have been found and other protein fractions, notably tyrosin and leucin, in the urine of some, and only some, cystinurics.

From this it would appear that what we call cystinuria, i. e. the excretion of cystin in the urine, is only the warning sign of an anomaly of protein metabolism of far wider range, which involves varying numbers of protein fractions in different cases.

It would seem also that cystin is the first fraction to be involved, but even this is uncertain, since, in the absence of cystin, with its characteristic crystalline deposits, the presence of tyrosin or leucin, and still more of the diamines, is likely to be overlooked. Nevertheless, it will hardly be doubted by those who have investigated cases of cystinuria, that in a considerable proportion of such cases cystin is the only protein fraction which is excreted unchanged in the urine.

The phenomena observed suggest that there is missing in the cystinuric an *enzyme or similar agent* which is concerned in the desamination of the protein fractions, and that in consequence of the lack of it the stripping off of the amino-groupings from the amino-acids of some part of the proteins of the diet is not carried out, as it usually is at an early stage of protein catabolism. It would seem, further, that in consequence of the failure of the process at that stage, the protein fractions involved escape the further destruction which they normally undergo.

As far as is yet known, the presence in the blood and tissues of the unchanged amino-acids has no effect which can be described as toxic, and it would appear that the troubles to which cystinurics are exposed are wholly due to the insolubility of cystin and its consequent deposition, in crystalline form, in undesirable situations. Obviously a compound so insoluble in acid media is eminently unsuited for excretion by animals whose urine is normally acid. Because of this insolubility the cystinuric man, although he may appear to be *in perfect health, lives with the sword of Damocles* suspended over his head. In Hutchinson's words, he has 'a peculiarity of health, giving proclivity to a definite form of disease'.

The special affliction of the cystinuric is the formation of urinary calculi, which in some instances attain to a large size, and in others are formed in very large numbers in the kidneys. In a few instances there have

been found, in the bodies of young infants who have died in a marasmic state, and some of whom were not known to be cystinuric during life, multiple deposits of crystalline cystin throughout the viscera.

Yet the cystinuric may go through life unaware of his peculiarity, and free from any calculous troubles. Thus several members of a family may all excrete cystine and show the deposits of hexagonal crystals in their urine, but it may be that only one of them will suffer from stones, and may form a number of stones in succession. It is obvious that there must be some external factor derived from the environment which thus discriminates between members of a family in all of whom the constitutional factor is present. Clearly the answer to be returned to the question what this influence is, has most important bearings upon the pathology of calculi in general.

Naunyn's work upon biliary calculi, and observations on cystinuric subjects, leads to the belief that it is to a local infection of the urinary tract, such as frequently occurs, that the inception of stone formation is to be ascribed. In the family of cystinurics the urine of the calculus-forming member alone may be infected with bacillus coli, but it must not be forgotten that such infection may be secondary to calculus formation. Some attempts, on Naunyn's lines, to find bacilli in a solution of the nucleus of a cystin calculus have hitherto failed, although the ready solubility of cystin in an alkali might be expected to facilitate such a search.

facts. As the knowledge of gout goes back to the beginnings of medicine, so also does the recognition of its hereditary transmission. We all know of families some members of which develop gout at unusually early ages, and which include many victims of the malady. Thus, a man whose father and paternal grandfather had both suffered severely, had his first attack of orthodox gout in the great toe at the age of twenty. His two brothers and three sisters all suffered from true gout, and a son of one of his sisters had gout at the age of sixteen, whilst a schoolboy. This is, of course, a very extreme example. It would seem that if gout is inherited as a Mendelian characteristic, it is a dominant one. It is a matter of common experience that gouty attacks are much less often seen to-day than was the case fifty years ago, and this is as true of hospital practice as of that amongst people in more comfortable circumstances. This cannot be wholly explained by a change of fashion in nomenclature, in consequence of which many cases which would have formerly been called gouty, are assigned to other classes, and it would rather appear that changes of diet and modes of life render the exciting causes of the manifestations of gout less prevalent.

The study of the pathogeny of gout is beset with peculiar difficulties, and despite all the work which has been expended upon it since the detection of uric acid in the blood of gouty people in the middle of the last century, no outstanding advance towards the solution of the problem has been made. A concensus of opinion

however much they may try to do so, whilst others cannot escape it, however hard they try not to provoke it. The comparatively late age at which, with few exceptions, the onset of the disease occurs suggests that the underlying error is not, in itself, seriously detrimental to its subjects, but that it renders them unduly susceptible to external influences. Unless such influences come into play the gouty man may escape the manifestations of his malady, and it can hardly be doubted that many who inherit the susceptibility do actually escape.

There is no conclusive evidence that uric acid and the urates as such exert any toxic influence upon the tissues, and there is strong evidence that the pathological vice of sodium biurate, like that of cystin, is its scanty solubility, and its tendency to be deposited in crystalline form in the tissues, and especially in cartilage. It is permissible to suppose that the conditions which ensure the holding in solution of the urate are, in the gouty subject, taxed to the full, and that a variety of external influences may precipitate attacks.

In a given community the prevalent mode of life and the environment undoubtedly influence the frequency of gouty attacks to a remarkable extent, but that does not imply that they influence the number of potentially gouty individuals in the community.

The manifestations of gout are much more frequently seen in cities than in rural areas, and the prevalence of the disease in imperial Rome, and in other cities in which much luxury prevails is a notorious fact; but it is

nowadays favours the view that the underlying trouble is a derangement of purin metabolism. Even if it should be proved that the accumulation of uric acid in the blood of gouty subjects is due to defective excretion by the kidneys, it may nevertheless result from a defect of purin metabolism, for the deficient excretion may be due to a shortcoming of the product to be excreted, rather than of the excreting organs.

It is a well-known fact that the excretion of endogenous uric acid is independent of changes of diet, but varies rather widely in different individuals; and a systematic study of the purin metabolism, and of the blood content of uric acid in members of gouty families from infancy upwards, might go far towards the elucidation of the nature of the malady. At present we have no such data to go upon.

If gout be due to an inborn error of metabolism, such as is here suggested, it cannot be looked upon as due, like other such errors, to a rare mutation which occasionally occurs *de novo*, but rather as based upon an alternative and slightly divergent path of metabolism met with in a large part of the total population. It is interesting to note that there appears to be a special liability of the male sex, not to be explained by the influence of diet and environment.

It is a matter of observation that some individuals fail to develop gout, in spite of diligent cultivation of those faulty habits which are supposed to conduce to attacks; in other words some are unable to acquire gout,

however much they may try to do so, whilst others cannot escape it, however hard they try not to provoke it. The comparatively late age at which, with few exceptions, the onset of the disease occurs suggests that the underlying error is not, in itself, seriously detrimental to its subjects, but that it renders them unduly susceptible to external influences. Unless such influences come into play the gouty man may escape the manifestations of his malady, and it can hardly be doubted that many who inherit the susceptibility do actually escape.

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these are the only joints which are damaged in walking, but defects of footwear doubtless contribute.

If the views here put forward are sound, gouty persons are subjects during the intervals between their attacks in which they may feel quite well, to 'a peculiarity of health' which gives proclivity to that particular form of disease; and just as a cystinuric may form no calculi, a gouty subject may never suffer from an actual attack of gout. It may be well to emphasize that the malady under discussion here has been true uratic gout, characterized by the deposition of crystalline sodium biurate in the tissues; a malady of which tophi in the ears may serve as a warning signs and serve as sure guides to diagnosis.

Much less is heard now than formerly of that congeries of discomforts and ailments which were formerly loosely classed as gouty, but which are now referred to other categories. The more exact indications afforded by the estimation of uric acid in a few drops of blood may reveal the gouty nature of troubles the true origin of which had not been suspected, and on the other hand corrects much loose classification. Nevertheless it must be remembered that increase of uric acid in the blood results from other causes besides gout.

The onset of the familiar osteo-arthritis of later life, with its erosion of cartilages, eburnation of bones, and formation of osteophytes, is often attributed to an injury. This is especially the case with the hip-joint disease of elderly people. Other manifestations of the malady,

Mendelian recessive, appearing in several children of parents who are usually normal, and of whom a large proportion are consanguineous, usually first cousins. The proportion of consanguineous parents is far greater than in the population at large.

The essential error is apparently a failure to effect the complete catabolism of the tyrosin and phenyl-alanin contained in the proteins of the food and tissues, and the consequent presence of an intermediate product of the metabolism of these aromatic fractions of proteins. The product in question, homogentisic acid, or hydroquinone-acetic acid, shares with many other similar aromatic compounds the property of blackening on oxidation, and hence the characteristic property of alcapton urine.

In the course of years the homogentisic acid in the tissues brings about a selective blackening of certain tissues, notably of the articular and aural cartilages, and so is induced a condition first recognized in the cadaver by Virchow as one of extreme rarity, and called by him ochronosis. Albrecht was the first to suggest that alcaptonuria might be a cause of ochronosis, and Osler described clearly the clinical picture of the condition as seen in several elderly alcaptonurics under his observation. These observations have been abundantly confirmed, and the blue coloration of the interior of the ears, due to the black cartilage showing through the skin, the presence of brown triangular patches on the sclerotics, and occasionally pigmentation of the skin of

clusive, the osteo-arthritis of alcaptonuria with ochronosis assumes a characteristic distribution and character which has been observed in all the recorded cases. So much is this the case that its presence might be recognized by one who knows, from the peculiar stance and gait of the sufferer.

The patient stands upon a wide base, and adopts a stooping attitude, due, as Söderberg has pointed out, to affection of the articulations of the spinal column. On the other hand it has been shown that there may be complete blackening of cartilages before there are any anatomical changes in the joints; and the signs of ochronosis become apparent to the clinical observer at a considerably earlier period than those of implication of the articular structures.

It would be wholly premature to suggest that the presence of an unusual chemical compound in the tissues and blood is the underlying factor in all cases of osteo-arthritis, but it seems clear that in some instances it is so, and that the lifelong presence of such a compound may produce its morbid effects only after the lapse of many years.

Among the exciting causes of disease a not unimportant place must be assigned to light, and at the present time when the beneficial action of light and ultra-violet radiation are attracting so much attention, it is well to be reminded that there are some to whom bright light is a poison, and that there is a class of maladies rightly named light diseases. One such is of

derivatives of haematin and haemoglobin, and to have preceded the blood pigments in the evolutionary chain. Moreover, they are to be obtained from vegetable as well as animal sources, and even from yeast.

A pigment of this group, called by Hans Fischer copro-porphyrin, because he first identified it in faeces, is present in minute traces in the urine of normal human beings; and it is tempting to imagine that similar traces present in the tissues of the average man may play an important part in connexion with the physiological action of waves of short length.

Following the administration of certain drugs over long periods, of which drugs sulphonal has been the chief offender, there occasionally develops a form of acute poisoning, often fatal, of which the excretion of porphyrins, in quantity sufficient to colour the urine a deep red or brown, is a conspicuous sign. Curiously enough the patients are almost always women. A similar, but less fatal porphyrinuria is seen occasionally as a symptom of disease, apart from the use of drugs. Except in a case recorded by Haxthausen in which luminal had been taken over a long period, and the red urine was also of some standing, no skin affection due to exposure to light has been observed in such cases, in which the porphyrinuria is usually transient, or merely an event in a fatal illness.

In some rare instances porphyrins are present in abundance in the *urine* and faeces from birth onwards. The dark red urine is the warning sign of this anomaly,

the ears and nose and even blindness from the implication of the cornea in the eruption. Nor is that all; the deeper tissues also are affected, and there result deformities of the hands with stiffness of the fingers and atrophy of the terminal phalanges. Another remarkable effect is deep staining of the bones, and in some cases of the milk teeth, and also those of the second dentition, by porphyrin.

On the other hand it seems certain that porphyrinuria is not the only cause of hydroa vacciniforme, any more than alcaptonuria is the only cause of osteo-arthritis, nor that it is even its commonest cause. In cases clinically similar there has been no excess of porphyrin in the urine; but it is significant that when cases of hydroa are collated both the sex incidence and type of heredity in the whole series resemble closely those of the porphyrinuric cases when taken alone. It may well be that the cases without porphyrinuria have their origin in some other metabolic error, or in several such, and that the sensitivity of porphyrinurics to light is only a particular instance of a much wider phenomenon.

The light-sensitizing power of the porphyrins has been proved by Hausmann and others by experiments on mice and on protozoa, and by the daring experiment of Mayer Betz upon himself, but hitherto it has proved difficult to reproduce the exact conditions needed for the development of the particular skin-eruption hydroa vacciniforme.

Just as it is possible to produce a form of ochronosis

character, and, as such, difficult to eradicate from a stock. It can hardly be doubted that this is due to the absence of an enzyme concerned with the coagulation of the blood.

It might be objected that the conditions spoken of in this chapter are extremely rare, and that it is unsafe to draw any conclusions from them as to pathogeny in general. Yet if it be granted that every human being has his chemical individuality, as well as his individuality of form, we may well suppose that, seeing how conspicuous are the effects of the more pronounced departures from chemical type, the minor differences between any two of us may play important if less conspicuous parts as inborn factors in disease.

As was mentioned, Gaucher's disease may form a connecting link between tissue defects and inborn metabolic errors, and it is clear that a chemical defect may bring in its train highly selective damage to particular kinds of tissues.

There can be little doubt that, as time goes on, more and more inborn errors of metabolism will be brought to light; but it is to be hoped that a too ready application of that term will be avoided. There is danger lest it should be employed without any adequate reasons, and to quote Germain Sée once more, as merely 'un mot pour masquer notre ignorance'.

An important suggestion has been put forward by A. Hurst,[1] namely, that constitutional achlorhydria,

[1] *Brit. Med. Jour.*, 1927, i. 866.

nature of the external factors is obscure. There are, on the other hand, many diseases in which the position is reversed, and the external factors are the most obvious and best defined. Without the tubercle bacillus there can be no tuberculosis, and without the plasmodium no malaria.

Nevertheless it must never be forgotten that it is not only in causing predisposition that internal factors are concerned; but also, that upon the patient's constitution depends the form which the morbid syndrome assumes. As Sydenham[1] wrote, nearly three hundred years ago: 'a disease, however much its cause may be adverse to the human body, is nothing more than an effort of Nature, who strives with might and main to restore the health of the patient by the elimination of the morbific matter.'

The exogenous diseases, as they may be called, are the most important of maladies, for they are responsible for the great bulk of human sickness, and for the largest part of the death-roll. In any medical ward in a hospital sufferers from infective diseases occupy most of the beds, and of such maladies tuberculosis, in its various forms, rheumatic fever and its sequels, and the troubles attributable to the pneumococcus and the streptococci are most abundantly represented. So it has come about that, in recent years, the importance of the parts played

[1] Medical Observations concerning the History and Cure of Acute Diseases (*Works of Thomas Sydenham*, translated by R. G. Latham, 1848, i 29).

cerned in their working. Most of them are known to us only by single properties; just as for many years the element helium was known to us only by its line in the yellow of the solar spectrum, and adrenalin only by its effect upon blood-pressure.

It is not even certain whether the formation of an antibody is a chemical reaction which follows inevitably from the entrance into the body of a certain antigen; just as effervescence results whenever an acid is added to a solution of a carbonate; or whether the chemical reaction involved has been elaborated by an age-long process of evolution, to meet the special emergency when it arises.

The investigator engaged upon the synthesis of organic compounds can confidently expect that if he follows a certain line of procedure he will obtain a compound the properties of which he can foretell, although it may never previously have existed. So also, when a harmful aromatic compound enters the human body it is combined with sulphuric acid, and excreted as a harmless aromatic sulphate, and when an acid is administered to a carnivorous animal it is neutralized by ammonia, whereas in a vegetivorous animal, whose food is rich in fixed alkali, this mechanism is not required to protect the fixed alkalies of the tissues, and has not, apparently, been developed.

On the other hand, when Baumann administered brom-benzene to a dog the animal excreted a mercapturic acid, a derivative of cystin, and in this form got

that we are constantly exposed to infections which fail to produce illness, but nevertheless call into play the protective mechanisms to counter them, with the result that a greater or less degree of immunity is acquired by individuals who are unaware that they have been exposed to the specific infection concerned. Furthermore, it is well established that maternal antibodies in the circulation of infants may confer an immunity during the early months of an infant's life. Consequently, when it is attempted to differentiate true inborn, or natural, immunity from such immunity as has been acquired after, or even before, birth the inquirer is in like position to one who listens to a wireless programme which is seriously obscured by heterodyne transmissions.

There is strong evidence that a community may acquire, in the course of time, a relative immunity from an infection to which it has been long and continuously exposed; whereas another community, not so protected by secular exposure, may, when the disease in question is introduced into it, suffer in wholesale numbers and from attacks of extreme severity and fatality. This may be due to acquired immunity produced by continual minor infections, or, as some think, and as Archdall Reid[1] so strongly urged, to raising of the level of protection by the weeding out of the more susceptible members by natural selection.

The clinical evidence of the existence of inborn im-

[1] *The Laws of Heredity*, 1910.

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tioned in an earlier section, the statistical investigations of the incidence of tuberculosis by Karl Pearson, Stocks, and Govaerts show a somewhat higher incidence of that disease in individuals in whose family it has occurred in previous generations, than in those whose family history presents a clean bill of health in that respect.

Obviously a definite test of susceptibility to infection offers the best chance of gaining reliable information regarding the existence or otherwise of inborn natural immunity to infective maladies, and in this connexion Schick's test of liability to diphtheria holds out the greatest promise of usefulness. If it can be shown that immunity from diphtheria conforms to some definite scheme of heredity, such evidence will be of special importance, for the risk of confusion with acquired immunity will be excluded. However, in the opinion of some who are well qualified to judge, the response to the question which the Schick test supplies is not unequivocal.

The test in question indicates the presence in the blood or tissues of the individual to whom the test is applied of diphtheria antitoxin, or at least his power of producing the antitoxin with ease.

H. and L. Hirszfeld[1] have carried out an elaborate investigation upon a large number of families and of individuals, both with the Schick test and with the Dick test of susceptibility to scarlet fever. These in-

[1] *Klin. Wchnschr.*, 1924, iii. 2084; *Ztschr. f. Immunitätsforsch.*, 1927–8, liv. 81; *Lancet*, 1919, ii. 675.

Here also are traces of that enigmatical sex-linkage, such as is seen in the metabolic errors, but in this instance the advantage lies with the males, who are less liable than females.

Clinical evidence points to a greater liability to diphtheria of females, and observations with the Schick test tend to confirm that impression. There is similar support for the belief, based upon clinical observation, that some races of mankind are more liable than others to acquire diphtheria.

S. F. Dudley,[1] in a critical review of the whole subject in which the findings with the Schick test, and the inferences based upon them, are subjected to a searching criticism, writes as follows: 'The evidence on the whole seems to favour the hypothesis that the potentiality of responding to antigenic stimuli from the diphtheria bacilli in the environment is greater in the average male than the average female. If this be so, susceptibility to diphtheria is to some extent a real, hereditary, sex-linked character.'

Again: 'A general survey of the evidence does undoubtedly suggest that a small percentage of the population are born with genetic defects in their potentiality to form diphtheria antitoxin, but that this hereditary factor has an insignificant bearing on the degree of immunity possessed by a community as a whole, compared with the concentration, distribution, and persistence of diphtheria bacilli in the environment.'

[1] *Quart. Jour. Med.*, 1928–9, xxii. 321.

Strictly speaking the term idiosyncrasy should be used to cover the whole ground of our individual differences, as co-extensive with our personalities. Jonathan Hutchinson, in his *Pedigree of Disease*, includes under the name even such structural anomalies as coloboma of the iris and cleft palate, and H. D. Rolleston,[1] in a recent monograph on idiosyncrasies, includes a psychological group, in which an idea or emotion, such as does not upset the average man or woman, brings about most unexpected reactions.

The peculiarities here to be considered cover a much more limited field, for in medical parlance the name idiosyncrasy is commonly applied to exceptional responses, on the part of exceptional individuals, to stimuli which are insufficient to produce any conspicuous effects in the great majority of members of the human race. Such stimuli are often applied in the forms of articles of diet or particular drugs, the pollen of particular plants, or the exhalations of particular animals.

Rolleston defines an idiosyncrasy as 'an abnormal reaction in an otherwise normal person, which may be either, on the one hand, greatly exaggerated, or, on the other hand, greatly diminished; more briefly it may be described as an unusual physiological personal equation'. The inclusion in this definition of what may be called negative idiosyncrasies is of special interest. It can hardly be doubted that there are variations to both sides of the average line, and that there are persons who

[1] *Idiosyncrasies*, 1927.

sented by the anaphylactic guinea-pig bears little outward resemblance to that manifested by an anaphylactic dog.

Anaphylaxis, properly so-called, is an artificial or adventitious state, which results from the injection of a protein into an animal which has previously been sensitized by the administration of a dose of the same protein. Nevertheless, certain of the symptoms which enter into the composition of the anaphylactic syndrome, such as rashes, usually urticarial, gastric disturbances, and respiratory embarrassment, are met with not only in anaphylactic states, but also in connexion with many of the human idiosyncrasies as regards drugs, foodstuffs, pollens, and animal emanations.

That some individuals are far more liable than average people to respond injuriously to such provocations is an undoubted fact, and it is reasonable to ascribe their sensitivity to the presence in their tissues of an antibody, ready to combine with the antigen when it comes their way. Indeed, Prausnitz and Kuster[1] detected such substances, which they called 'atopic reagins', in the blood of hypersensitive individuals, and by injecting blood from such an atopic individual into the skin of a normal man they rendered the injected area of the skin of the recipient, and that area alone, sensitive to the foodstuffs or pollens which gave rise to allergic reactions in the donors of the blood.

There is strong evidence that in the subjects of the

[1] *Zentralbl f Bakt., Abth. 1 (Originale)*, 1921, lxxxvi. 160.

respond less vigorously to the stimuli mentioned than do the bulk of human beings. However, we should expect that such negative idiosyncrasies would be more difficult to study than are the converse positive peculiarities.

The idiosyncrasies are of special importance from the point of view set out in this essay, for nowhere are our individualities more clearly manifested than in such wide departures from type.

Whereas we might hesitate to label an attack of giant urticaria, following the eating of honey, and recurring whenever honey be eaten, as a disease in the ordinary sense of that term, it is not possible to draw any sharp dividing line between such attacks and morbid pictures to which no one would hesitate to apply the name. Some varieties of asthma fall into the one, and some into the other category.

A large number, perhaps the largest number of idiosyncrasies, are manifestations of hypersensitiveness, and their symptoms are such as characterize allergic or anaphylactic states, which result from the introduction of foreign proteins into the organism.

Immunological investigations have shown that the intrusive substance, the so-called antigen, encounters, chiefly in the tissue cells, a substance which is antagonistic to it, an antibody, and to the effects of their encounter the observed phenomena are ascribed.

These symptoms differ in conspicuous ways in animals of different genera; the suffocative syndrome pre-

sented by the anaphylactic guinea-pig bears little outward resemblance to that manifested by an anaphylactic dog.

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The hereditary transmission of hay-fever and of asthma is well recognized; angioneurotic oedema has been traced through five generations of a family in which the condition proved fatal in a number of cases, and even so highly specialized an idiosyncrasy as intolerance of egg-albumin has been recorded as occurring in three generations of a family.

The simplest of all forms of allergic idiosyncrasy is that known as 'factitious urticaria' or 'dermatography'. Here the exciting cause is no introduction of a foreign protein or other substance, but a mere mechanical pressure often of a very slight kind. Anything written or drawn upon the skin of a subject of this anomaly, even by gentle pressure with a pencil or other blunt point, stands out, after a short time, in the form of raised wheals. The phenomenon is an exaggeration of normal happenings, but provoked by a pressure which would cause but insignificant manifestations in an average individual.

The series of phenomena observed in subjects of factititous urticaria, and in less pronounced degree in average individuals, has formed the subject of a masterly investigation by Thomas Lewis[1] and his fellow workers. The initial flush, due to dilatation of capillaries, the more lasting flare around the seat of pressure, which is due to relaxation of the adjacent arterioles, and the eventual wheal, are also members of the anaphylactic syndrome, and are signs met with in a number of other

[1] *The Blood Vessels of the Human Skin, and their Responses*, 1927.

allergic idiosyncrasies the hypersensitivities which they exhibit are inborn peculiarities in most, if not in all cases; nevertheless, as in not a few hereditary morbid conditions, their manifestations may be postponed, and may not be in evidence during the early years of life or even longer. Thus, an article of diet which was previously taken with impunity, may be found, in later life, to elicit an allergic response. Conversely it is undoubtedly the case that an idiosyncrasy to a particular antigen may disappear as an individual grows older, probably as the result of a process of desensitization.

There is a large amount of evidence of the hereditary transmission of hypersensitivities; but it would appear that members of different generations of a family, and even members of the same sibship of brothers and sisters, *although hypersensitive, in the sense under discussion,* do not always react exceptionally to the same antigens.

Cooke and van der Veer,[1] in America, found that hypersensitivity could be traced in the antecedents of 48·5 per cent. of a group of 504 individuals who themselves exhibited some form of hypersensitivity, but in the antecedents of only 14·5 per cent. of normal individuals. The same investigators found that the allergic symptoms tended to make their first appearance between the ages of 20 and 26 years in persons having only one hypersensitive parent, whereas in children both of whose parents were hypersensitive, the symptoms appeared at 5 years or earlier.

[1] *Jour. Immunol.*, 1916, i 201

explanation as accounting for all the known facts. He points out that by any of the earlier conceptions of the process at work, it was difficult to explain why, in each species of animal, only those cells which are normally sensitive to histamine appear to be sensitive also to the foreign antigen, and respond to its injection.

If Lewis's explanation be adopted this need not be assumed. It is only necessary to suppose that from whichever cells histamine may be set free, by the union of antigen with antibody within them, those cells which are normally sensitive to histamine take part in the production of the obvious reaction which results.

On this theory we have not to deal with an undue sensitivity of certain cells to histamine, but with excessive liberation of that substance, either into the parts adjacent to the seat of its liberation, or when, as in the dog, the setting free of histamine results from anaphylactic damage to a large viscus, such as the liver, the discharge is into the general blood-stream. So it comes about that the liberated histamine produces its characteristic response in cells which are normally sensitive to that base, but which are not themselves affected by the antigen. In this way may be explained the striking differences in the anaphylactic syndrome, as seen in animals of different species, such as the dog and the guinea-pig respectively.

As Dale points out further: 'We may picture the anaphylactic shock, therefore, as the result of cellular injury due to the intra-cellular reaction of the antigen

kinds of idiosyncrasy, elicited by other causes than mere pressure.

Lewis, in the course of his work, has traced the production of the flush, flare, and wheal to the liberation by the injured cells of a substance which he calls the 'H substance'. This initial was chosen because of the similarity of the physiological action of the H substance to that of histamine, a base derived from histadine by removal of a CO_2 group, and which was originally found in the tissues by Dale and Barger. H. H. Dale[1] has since advanced strong reasons for taking a bolder view, and for the identification of the H substance with histamine, which base is known to be present normally in the tissues.

The expression 'liberation of histamine' is a somewhat guarded one, but it is more probable that, under the influence of agents which damage the tissue cells, the preformed histamine which they normally contain escapes into the circulation, than that histamine is formed in excess, as a result of the damage, and is thrown out for any protective purpose.

Seeing that the same triple response, the flush, the flare, and the wheal, figures amongst the anaphylactic reactions in healthy skins, Lewis came to the conclusion that the union of antigen and antibody in the cells in which it occurs liberates the preformed H substance, just as a mechanical injury does; and Dale regards this

[1] 'Croonian Lectures on some Chemical Factors in the Control of the Circulation', *Lancet*, 1929, i. 1285

explanation as accounting for all the known facts. He points out that by any of the earlier conceptions of the process at work, it was difficult to explain why, in each species of animal, only those cells which are normally sensitive to histamine appear to be sensitive also to the foreign antigen, and respond to its injection.

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no more the cause of anaphylaxis and allergy than gunpowder is the cause of war. An explanation has still to be sought for the extraordinary hypersensitiveness of the cells of certain individuals to injuries of certain kinds, and the readiness of those cells to set free histamine under provocation which fails to produce such results in the cells of the average man.

It is, at least, highly probable that the explanation of allergy is to be found in the chemical individuality of the subject, and of those of his cells which are damaged by antigen, seeing how discriminative is the action of the causative agents at work. If there were merely a greatly exaggerated sensitiveness to histamine of the cells which are normally sensitive to it but in a far lesser degree, we should expect that disturbance would be induced by any of the recognized causes of the histamine syndrome, from slight mechanical pressure upwards; but this is far from being the case. Therefore it must be assumed that the cells of a subject of factitious urticaria are not unduly sensitive to histamine, but that they liberate that substance with undue readiness, whereas in the great majority of human beings the histamine syndrome produced by pressure upon the skin is far less pronounced, and requires greater pressure for its induction.

As a rule, of the known causes of allergy only one is effective in any particular case.

It will be remembered that Cooke and van der Veer found that in families containing hypersensitive mem-

bers, the exciting cause of the manifestations may not be the same in all the members, but in some cases sensitiveness to a particular *antigen, such as egg albumin*, is manifested by members of successive generations of a family. It would seem that the essential factor is the chemical or physico-chemical interplay of antigen and antibody in the cells of the subject, as the result of which histamine is liberated from the damaged cells. What is inherited is an undue liability to such cellular protests against some particular antigen or antigens, but not always the same ones.

Examples of such selective idiosyncrasies are quoted by all authors who have written upon the subject. The *present writer, who has not, to his knowledge, any* excessive sensitivity to any other flower or plant, and who does not suffer from hay-fever, is unable to stay in a room with the flowers of the orange-coloured buddleia without experiencing general discomfort and breathlessness, but without any stridor. The purple buddleia, on the other hand, has no such effect.

A member of a former generation of his family could not, when young, eat any fish of the family of the pleuronectidae, sole, plaice, turbot, halibut, and the like, without experiencing severe gastric symptoms; but from middle life to extreme old age, she could eat such fishes without ill effect.

All men are subject to some allergic effects, upon adequate provocation, and it would be difficult to suppose that whereas *some are much more sensitive than*

the average man, there are not others who are decidedly less sensitive. It is naturally more difficult to bring forward examples of such negative idiosyncrasies; but perhaps the best known is the scanty response of some individuals to bites of such insects as fleas and to the stings of nettles.

From a mere idiosyncrasy towards a particular antigen there are all stages to what are known as the allergic diseases; of which asthma is the most important, although angio-neurotic oedema is more fatal. Such diseases have been discussed widely in recent years, on the Continent by Storm van Leeuwen,[1] in this country by Hurst,[2] and in America by Coca,[3] Cooper, and others.

Idiosyncrasies to drugs are sometimes of the allergic kind, as when a drug such as quinine or antipyrine gives rise, whenever taken, to an urticarial rash, with or without attendant vomiting. In some cases a drug produces an effect quite unlike its usual action, as when opium causes excitement; but more usually the normal action of the drug is induced by unusually small doses, or on the other hand an abnormal degree of tolerance may be manifested.

Every drug which has a definite physiological action acts as a poison when taken in excessive doses, but in different individuals and in animals of different species

[1] *Allergic Diseases*, 1925.
[2] A. F. Hurst, *The Constitutional Factor in Disease*, 1927.
[3] Coca, *Essentials of Immunology*, 1925.

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All men are subject to some allergic effects, upon adequate provocation, and it would be difficult to suppose that whereas some are much more sensitive than

their subjects, and the chemical structure of their tissues. Their tendency to family occurrence, and their intimate relationship to such hereditary maladies as angioneurotic oedema and asthma, suggest strongly that idiosyncrasies are inborn peculiarities, even in cases in which they do not manifest themselves in the early years of life.

the dose per kilogram needed for the production of such effects differs somewhat widely. The same is true of children and adult men and women respectively, as witness the well-known tolerance by children of belladonna, and their relative intolerance of opium.

Much experimental work has been carried out, by Clark[1] and others, upon the tolerance of drugs by animals, and a mass of evidence regarding this matter was brought together, in a critical review, by J. A. Gunn[2] in 1923. Some of the protective methods directed to saving the tissues from the ill effects of chemical poisons were spoken of in an earlier section, but it should be mentioned further that there is reason to believe that the destruction of drugs within the body is brought about in not a few cases by enzyme action; it would appear that in the cases of atropine, morphia, and strychnine amongst other alkaloids, the liver is the organ chiefly instrumental in their destruction. It may well be that, as Gunn suggests, the ferments concerned are usually occupied in dealing with ordinary products of metabolism, rather than that they lie in wait in the tissues in the hope that some day their appropriate alkaloid may come along.

It will have been seen that all that we know of the nature of idiosyncrasies, either allergic or other, suggests that the factors which bring about their manifestations are intimately connected with the chemical life of

[1] *Quart Jour Exper Physiol.*, 1912, v 185

[2] *Physiol Rev.*, 1923, iii 41

are two sets of factors at work in the formation of the morbid picture, namely internal or constitutional factors, inherent in the sufferer and usually inherited from his forebears, and external ones which fire the train. In some instances, and especially in infective diseases, the external factors dominate the picture, in so far as the causation of the trouble is concerned, but the symptoms observed represent the response of the patient to the assault of the invaders. In some other maladies, such as the hereditary abiotrophies of the neuromuscular system, the external factors are so little in evidence that they are apt to be overlooked. Between these two extremes various intermediate stages are met with.

The constitution of a man is the sum of *all* his qualities, his bodily form, the structure of his tissues, his coloration, height, weight, blood-pressure, and body temperature; as well as his mental and moral qualities, functional processes, and tricks of gesture and action.

In all or some of these respects each man differs from all his fellows, for even uniovular twins are not exactly alike.

The differences between the various species of animals in their chemical build and chemical processes are well known, and it follows, and can indeed be demonstrated, that the individual members of a species are likewise possessors of chemical individuality; that each is built up of slightly different materials from his fellows, and leads his own chemical life. Seeing that all the factors in the constitution of the future man are represented in

Epilogue

Mehr und mehr wirt die Krankheitslehre zur Konstitutionspathologie: zwar wirkt die Umwelt auf den Körper ein; aber Art und Grad der Wirkung hängt von der angeborenen Anlage ab.—WILHELM HIS. 1918.

THE subjects which have been touched upon in the course of this essay, as illustrating the importance and the nature of the inborn factors in disease, cover so wide a field, and throw light upon the subject from such different angles, that it will be well to take stock, in a brief concluding review, of the general conclusions arrived at or suggested, of the way in which the several pieces of the puzzle can be fitted together.

It was pointed out, in the historical introduction, how, starting from the recognition of morbid predispositions, there were built up theories of diatheses which assumed various forms, but which were all impaired by the lack of knowledge, in the days in which they were propounded, of fundamental problems upon which modern science has thrown fresh light Hence it became obvious that in order to arrive at any sound conclusions on the liabilities of individuals to, and their immunity from certain maladies, it was necessary to approach the subject *de novo* in the light of that more recent knowledge, whilst recognizing fully that in fifty years a still more ample knowledge will doubtless displace many of our own conclusions in turn.

The further nosology is pursued, the more clearly does it emerge that in every case of every malady there

which he has developed that improvement of the race is possible.

Many of the difficulties which surround the phenomena of heredity have been removed in recent years, and Mendel's theory serves to explain the skipping of one or more generations, the occurrence of an anomaly in several children of parents who are themselves apparently normal, and the remarkable sex-linked inheritance of haemophilia.

In the course of ages the human organism has become remarkably well adapted to the conditions in which it lives, and it is able to adapt itself to somewhat wide changes of environment; as witness man's power to live in the polar regions or in the tropics, on the mountain side or below the sea-level. Nevertheless, that condition of adjustment which we speak of as health is maintained only by a continuous struggle; it is a dynamic, not a static state, and there is truth in the popular phrase, for a man *keeps* rather than *remains* healthy.

Man has to struggle against his own individual shortcomings upon the one hand, and against physical agents, chemical poisons, and the attacks of pathogenic organisms on the other hand.

What we describe as diseases are groups of symptoms, forming clinical and pathological pictures which portray that struggle. Many such pictures represent the reaction of the organism to the attacks of morbific agents; its attempts, which happily are often successful, to beat off or destroy the invaders.

the chromosomes of the germinal cells from which he shall spring, it can hardly be supposed that such diverse potentialities as are foreshadowed in structures so minute, and so little different from each other as are the germinal cells of creatures of different species, can have *other than a molecular representation.*

If this be so, it can hardly be doubted that variations in the chemistry of the chromosomes of the germinal cells are the starting-points of mutations great and small. Upon these mutations natural selection is continually at work, ensuring the persistence of those which make for the welfare of the organism and the species, and weeding out those which are detrimental. It is even difficult to escape the conclusion that upon the chemical structure of the chromosomes depend even the structure and forms of the creatures which spring from them, and the anatomical deviations from type which some of them display. How profound an influence chemical products can exert upon form is shown in the workings of some of the hormones

A particular mutation may recur, apart from inheritance, just as the same chemical reaction will be repeated whenever the same reagents come together under suitable conditions. We are not obliged to suppose that all those who exhibit a mutation, even a very rare one, are, to whatever the race they may belong, members of a single family.

On the other hand, it is because an individual is able to hand on to his descendants some favourable mutation

which he has developed that improvement of the race is possible.

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What we describe as diseases are groups of symptoms, forming clinical and pathological pictures which portray that struggle. Many such pictures represent the reaction of the organism to the attacks of morbific agents; its attempts, which happily are often successful, to beat off or destroy the invaders.

Unquestionably disease has played, and is playing, a very important role in the process of evolution, and is a potent agent for the weeding out of those least able to survive. But as man has developed, the process of survival of the fittest, in Nature's sense, has received a check, as far as the human race is concerned. The ideals of mutual help, the care devoted to the maimed and mentally deficient, and indeed the entire arts of medicine and surgery, are marshalled in direct opposition to the struggle for existence, as it is seen in the lower animals. Clearly, it is to his brain rather than to his muscles that man owes his survival and his high place in Nature.

When we speak of a normal man we mean one who does not depart, in any conspicuous respect, from the average of the race. That average cannot be represented by a sharp line, but by a series of dots, some to one and some to the other side of an imaginary line. Some of us deviate from the normal to our benefit, and some of us to our detriment.

The various races of mankind, and groups of people who may, or may not, be descendants of common ancestors, show constitutional resemblances, including likenesses in face and form, as well as in mental qualities and dispositions. With these resemblances are often linked degrees of liability to suffer from particular diseases. Hence the study of bodily form by anthropometric methods can give intimations of the *maladies from* which individuals are likely to suffer; but the peculiarities of outward form are in no sense the causes of disease,

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but are the labels indicative of particular morbid liabilities.

On the other hand, amongst the unnumbered differences of form which serve to distinguish each man from his fellows, there are some which may handicap him on his way through life, may lame him or disfigure him, and others which directly predispose him to disease. An abnormal mesentery may lead to strangulation of the intestine, an abnormal diverticulum may become the seat of inflammation or ulceration, a malformed cardiac valve may suffer too readily from infection. Yet such accidents are too uncommon to play any conspicuous parts in the aetiology of disease, nor is any important general inference to be drawn from them.

In some human families numbers of members exhibit anomalies of particular tissues, or tissues of certain groups, which are strongly suggestive of defects in the materials of which the affected tissues are constructed, or of the manner in which the materials are put together; as if Nature had descended to jerry-building. A conspicuous example is afforded by the highly hereditary kind of brittleness of bones, in which the defect of the connective tissues is made evident by undue translucency of the sclerotics which appear blue in colour because the black choroid shows through them. It is shown also in the fragility of the bones which are broken by slight injuries. Upon this congenital defect is engrafted, as time goes on, a progressive disease, otosclerosis.

In all probability minor defects of tissues are very common, and not only defects but also improvements upon the average standard. Various examples were alluded to in section vi of this essay. They are of widely different kinds, but in all some particular kind of tissue is implicated, and even when the trouble is not obvious at birth, that tissue appears to be unable to stand even the ordinary wear and tear of life. Of special interest are the maladies, hereditary, and sooner or later fatal, of the neuromuscular system, to which Gowers gave the name of abiotrophies. In them we see what Galton described as 'the steady and pitiless march of the hidden weaknesses in our constitutions through illness to death'.

Their subjects may appear to be in perfect health during their early years, and only show signs of their disease in later childhood, or even later. But their hereditary and family occurrence, which is specially well marked in that sex-linked recessive condition pseudo-hypertrophic muscular dystrophy, point clearly to an inborn defect. Although it is generally assumed that the tissues themselves are at fault in the abiotrophies, and that their power of resistance to the unavoidable minor accidents of life is so seriously impaired that, as Rosenbach put it, the ordinary use of the parts amounts to an injury, the possibility is not wholly excluded that the tissues involved may be damaged, or rendered sensitive to damage, by the presence in them of some metabolic product which progressively impairs their in-

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problems, and problems of the greatest importance because such maladies are responsible for the great bulk of human sickness, and take the heaviest toll of human life. In them the organism is called upon to wage an active fight against highly trained external enemies, whether bacteria, viruses, or protozoa, and the signs and symptoms which compose the pictures of such diseases are the evidences of that struggle.

Even against chemical poisons taken by mouth, or by other channels, there are some means of defence. Every active drug is a poison, when taken in large enough doses; and in some subjects a dose which is innocuous to the majority of people has toxic effects, whereas others show exceptional tolerance of the same drug.

Some chemical poisons are destroyed in the tissues, provided that the dose given be not too large, and others are combined up with substances to hand, and so rendered innocuous and got rid of.

Against bacterial invaders more subtle protective mechanisms have been evolved, some to destroy the invaders and others to render their toxins innocuous. The protective substances present in the blood and tissues, *antitoxins*, *agglutinins*, *opsonins* and the like, are undoubtedly chemical compounds, but as yet we know nothing of them save the properties from which they derive their names. When an invasion occurs the specific antibody is formed, if not already present, and an immunity is acquired which lasts for weeks, months, years, or even for the remainder of life.

tegrity. As yet there is little evidence in support of either hypothesis. The changes observed in the apparently unaffected muscles of dystrophic subjects may be degenerative rather than primary, but no abnormal chemical product has yet been detected in the tissues of patients with any of the conditions here spoken of as tissue defects.

It is highly probable that chemical defects, or errors of metabolism, are very common, although any individual error is rarely met with. Those which we know proclaim their presence in some obvious way, or are detected because they respond to often applied tests. Others which do not so advertise themselves may readily escape notice. For example, if the copper tests for detection of glucose were not in daily use in medical work, there is no symptom yet known by which the existence of that rare anomaly pentosuria could have been detected.

Presumably some chemical mutations are beneficial or at least harmless; but some render their subjects liable to morbid developments of particular kinds. To the victim of congenital porphyria light behaves as a poison, the cystinuric is always in danger of calculous troubles, and the alcaptonuric is wont to develop in late life an osteo-arthritis of characteristic kind and distribution. By the study of such anomalies one seems to approach very nearly the solution of some cases of morbid predisposition.

When we turn to the consideration of the infective maladies we find ourselves confronted by a new set of

role in the production of the allergic syndrome is secreted by the damaged cells, rather than leaks from them when they are damaged.

But allergy is, to all appearance, a chemical event, and the highly specialized effects of particular exciting substances, the pollen of a special plant or the exhalation of an animal of a particular species, point to a large personal element in connexion with such phenomena. Moreover, we can hardly doubt that in many, if not in all cases, the susceptibility is inborn. Such idiosyncrasies are apt to occur in several members of a family, but the exciting cause is not always the same in the different members of a family. In the grave diseases which pertain to the allergic group, such as asthma in some at least of its forms, and angioneurotic oedema which, when it affects the larynx, may cause death by suffocation, the hereditary factor is often strongly marked.

It might be claimed that what used to be spoken of as a diathesis is nothing else but chemical individuality. But to our chemical individualities are due our chemical *merits* as well as our chemical shortcomings; and it is more nearly true to say that the factors which confer upon us our predispositions to, and immunities from the various mishaps which are spoken of as diseases, are inherent in our very chemical structure; and even in the molecular groupings which confer upon us our individualities, and which went to the making of the chromosomes from which we sprang.

Apart from this natural process, the appropriate antibodies may be administered in the serum of an immunized animal, or their formation may be stimulated by a vaccine containing the toxin.

This, as was pointed out in an earlier section, greatly aggravates the difficulty of determining how far a natural immunity against infective diseases exists; for so many individuals have acquired immunity in one or other of these ways or even by exposure to contagion apart from any actual attack of the disease under investigation.

The clinical evidence of the existence of natural immunity, and also of unusual liability to particular maladies, is very strong, and is based upon the experience of many generations of medical men. It receives support from the results of statistical investigations of liability to tuberculosis for example, and from the results of the Schick test of liability to diphtheria. Yet such testimony gives a somewhat restrained answer. There is, moreover, testimony of clinical experience to the hereditary character of such immunities and liabilities.

Lastly, the so-called idiosyncrasies, disturbances of health out of all proportion to the external causes which provoke them, display the protest of the organism against the intrusion of some foreign substance, sometimes a drug, more often a foreign protein. It is not clear how far the phenomena observed in such cases have a protective purpose, as those of inflammation have; nor that the base histamine which plays a leading

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